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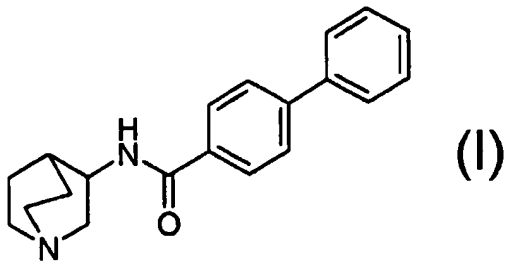
(54) Title: NOVEL BIARYLCARBOXAMIDES



(I)

(57) Abstract: A compound of formula (I), wherein A represents (II), (III), (IV) or (V), D represents oxygen or sulfur; E represents a single bond, oxygen, sulfur, or NR^{10}; R represents hydrogen or methyl; Ar^1 represents a 5- or 6-membered aromatic or heteroaromatic ring containing zero to three nitrogen atoms, zero or one oxygen atom, and zero or one sulfur atom; Ar^2 represents a 5- or 6-membered aromatic or heteroaromatic ring containing zero to three nitrogen atoms, zero or one oxygen atom, and zero or one sulfur atom or; an 8-, 9- or 10-membered fused aromatic or heteroaromatic ring system containing zero to three nitrogen atoms, zero to one oxygen atom, and zero to one sulfur atom; the aromatic rings Ar^1 and Ar^2 are optionally substituted with one or three substituents selected from: halogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, CN, NO_2, NR^1R^2, $CH_2NR^1R^2$, OR^3, CH_2OR^3, CO_2R^4, CF_3; R^1, R^2 and R^3 are independently C_{1-4}alkyl, aryl, heteroaryl, $C(O)R^5$, $C(O)NHR^6$, $C(O)R^7$, SO_2R^8 or R^1 and R^2 may together be $(CH_2)_jG(CH_2)_k$ where G is oxygen, sulfur, NR^9, or a bond; j is 2 to 4; k is 0 to 2; R^4, R^5, R^6, R^7, R^8, R^9, and R^{10} are independently C_{1-4}alkyl, aryl, or heteroaryl; or an enantiomer thereof and pharmaceutically acceptable salts thereof; with the provisos that: (1) if D represents oxygen, E represents a single bond, and A represents (II) and either Ar^1 or Ar^2 represents a pyrazole ring, then all optional substituents on the pyrazole ring shall be hydrogen; and (2) if Ar^1 represents a pyridine ring, Ar^2 represents an aryl ring, and A represents (II), then all optional substituents on the pyridine ring shall be hydrogen; and (3) formula (I) does not represent (a); processes for preparing them, pharmaceutical compositions containing them and their use in therapy, especially in the treatment or prophylaxis of psychotic and intellectual impairment disorders.

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NOVEL BIARYLCARBOXAMIDES

Technical Field

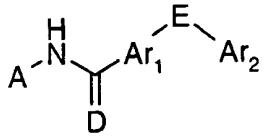
This invention relates to novel biarylcarboxamides or pharmaceutically acceptable salts thereof, processes for preparing them, pharmaceutical compositions containing them and their use in therapy. A further object is to provide active compounds that are potent ligands for nicotinic acetylcholine receptors (nAChRs).

Background of the Invention

The use of compounds which bind nicotinic acetylcholine receptors in the treatment of a range of disorders involving reduced cholinergic function such as Alzheimer's disease, cognitive or attention disorders, anxiety, depression, smoking cessation, neuroprotection, schizophrenia, analgesia, Tourette's syndrome, and Parkinson's disease has been discussed in McDonald et al. (1995) "Nicotinic Acetylcholine Receptors: Molecular Biology, Chemistry and Pharmacology", Chapter 5 in Annual Reports in Medicinal Chemistry, vol. 30, pp. 41-50, Academic Press Inc., San Diego, CA; and in Williams et al. (1994) "Neuronal Nicotinic Acetylcholine Receptors," Drug News & Perspectives, vol. 7, pp. 205-223.

Disclosure of the Invention

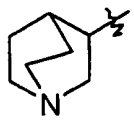
According to the invention, it has been found that compounds of formula I:



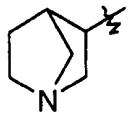
I

wherein:

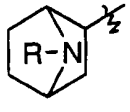
A represents:



II

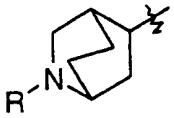


III



IV

or



V

D represents oxygen or sulfur;

E represents a single bond, oxygen, sulfur, or NR^{10};

R represents hydrogen or methyl;

Ar^1 represents a 5- or 6-membered aromatic or heteroaromatic ring containing zero to three nitrogen atoms, zero or one oxygen atom, and zero or one sulfur atom:

Ar^2 represents a 5- or 6-membered aromatic or heteroaromatic ring containing zero to three nitrogen atoms, zero or one oxygen atom, and zero or one sulfur atom, or;

an 8-, 9- or 10-membered fused aromatic or heteroaromatic ring system containing zero to three nitrogen atoms, zero to one oxygen atom, and zero to one sulfur atom;

wherein when Ar2 is unsubstituted phenyl, Ar^1 is not pyrazolyl;

the aromatic rings Ar^1 and Ar^2 optionally substituted with one to three substituents selected from: halogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, CN, NO_2, NR^1R^2, $CH_2NR^1R^2$, OR^3, CH_2OR^3, CO_2R^4, and CF_3; but if Ar^1 is phenyl and Ar^2 is quinolynyl, then Ar^2 is substituted with 0, 1, 2 or 3 substituents selected from C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, CN, NO_2, NR^1R^2, $CH_2NR^1R^2$, OR^3, CH_2OR^3 and CO_2R^4;

R^1, R^2, and R^3 are independently C_{1-4}alkyl, aryl, heteroaryl, $C(O)R^5$, $C(O)NHR^6$, $C(O)R^7$, SO_2R^8 or R^1 and R^2 may together be $(CH_2)_jG(CH_2)_k$ where G is oxygen, sulfur, NR^9, or a bond;

j is 2 to 4;

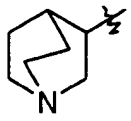
k is 0 to 2;

R^4, R^5, R^6, R^7, R^8, R^9, and R^{10}, are independently C_{1-4}alkyl, aryl, or heteroaryl;

or an enantiomer thereof, and pharmaceutically acceptable salts thereof,

with the provisos that:

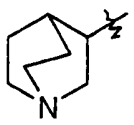
if D represents oxygen, E represents a single bond, and A represents:



II

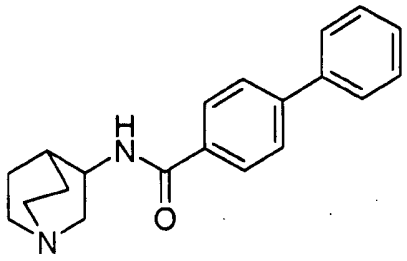
and either Ar^1 or Ar^2 represents a pyrazole ring , then all optional substituents on the pyrazole ring are hydrogen; and

if Ar^1 represents a pyridine ring, Ar^2 represents an aryl ring, and A represents:



II

then all optional substituents on the pyridine ring shall be hydrogen; and formula I does not represent:



are potent ligands for nicotinic acetylcholine receptors.

Unless otherwise indicated, the C_{1-4}alkyl groups referred to herein, e.g., methyl, ethyl, n-propyl, n-butyl, i-propyl, i-butyl, t-butyl, s-butyl, whether alone or part of another group, may be straight-chained or branched, and the C_{3-4} alkyl groups may also be cyclic, e.g., cyclopropyl, cyclobutyl. Alkyl groups referred to herein may optionally be substituted with one to three halogen atoms.

Unless otherwise indicated, aryl refers to a phenyl ring which may optionally be substituted with one to three of the following substituents selected from: halogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, NR^1R^2, $CH_2NR^1R^2$, OR^3, CH_2OR^3, CO_2R^4, CN, NO_2, and CF_3.

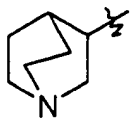
Unless otherwise indicated, heteroaryl refers to a 5- or 6-membered aromatic or heteroaromatic ring containing zero to three nitrogen atoms, zero or one oxygen atom, and zero or one sulfur atom, provided that the ring contains at least one nitrogen, oxygen, or sulfur atom, which may optionally be substituted with one or more substituents selected from: halogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, NR^1R^2, $CH_2NR^1R^2$, OR^3, CH_2OR^3, CO_2R^4, CN, NO_2, and CF_3.

Unless otherwise indicated, halogen refers to fluorine, chlorine, bromine, or iodine.

Pharmaceutically acceptable derivatives include solvates and salts. For example, the compounds of formula I can form acid addition salts with acids, such as the conventional pharmaceutically acceptable acids, for example, maleic, hydrochloric, hydrobromic,

phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric and methanesulfonic acids.

Preferred compounds of the invention are compounds according to formula I wherein A represents:



II

or an enantiomer thereof, and pharmaceutically acceptable salts thereof.

Preferred embodiments of the invention include compounds of formula I wherein D represents oxygen; or an enantiomer thereof, and pharmaceutically acceptable salts thereof.

Preferred embodiments of the invention include compounds of formula I wherein E represents a single bond; or an enantiomer thereof, and pharmaceutically acceptable salts thereof.

Preferred embodiments of the invention include compounds of formula I wherein E represents oxygen or NR^{10}; or an enantiomer thereof, and pharmaceutically acceptable salts thereof.

Preferred embodiments of the invention include compounds of formula I wherein Ar^1 represents a 5- or 6-membered aromatic or heteroaromatic ring containing zero or one nitrogen atom, zero or one oxygen atom, and zero or one sulfur atom; or an enantiomer thereof, and pharmaceutically acceptable salts thereof. Among these, compounds in which Ar^1 represents a benzene ring, furan ring or thiophene ring, are particularly preferred.

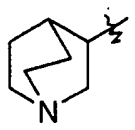
Preferred embodiments of the invention include compounds of formula I wherein Ar^2 represents a 5- or 6-membered aromatic or heteroaromatic ring containing zero to three nitrogen atoms, zero or one oxygen atom, and zero or one sulfur atom; or an enantiomer thereof, and pharmaceutically acceptable salts thereof. Among these, compounds in which Ar^2 represents a benzene ring, furan ring, thiophene ring, or pyridine ring are particularly preferred.

Preferred embodiments of the invention include compounds of formula I, wherein the aromatic ring Ar^1 is substituted with $-EAr^2$ and the carboxamide, or thiocarboxamide group, C(=D)NHA, but no further substituents; or an enantiomer thereof, and pharmaceutically acceptable salts thereof.

Preferred embodiments of the invention include compounds in which the -EAr^2 and the carboxamide or thiocarboxamide group, C(=D)NHA, substituents on Ar^1 are positioned in a 1,3-relationship relative to each other; or an enantiomer thereof, and pharmaceutically acceptable salts thereof.

Preferred embodiments of the invention include compounds of formula I wherein Ar^1 or Ar^2 is substituted with zero or one substituents selected from: halogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, CN, NO_2, NR^1R^2, $CH_2NR^1R^2$, OR^3, CH_2OR^3, CO_2R^4, and CF_3; or an enantiomer thereof, and pharmaceutically acceptable salts thereof.

Particularly preferred embodiments of the invention also include compounds of formula I wherein A represents:



II

D represents oxygen;

E represents a single bond;

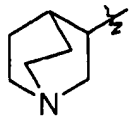
Ar^1 represents a 5- or 6-membered aromatic or heteroaromatic ring containing zero or one nitrogen atom, zero or one oxygen atom, and zero or one sulfur atom, and most preferably represents a benzene ring, furan ring or thiophene ring;

Ar^2 represents a 5- or 6-membered aromatic or heteroaromatic ring containing zero to three nitrogen atoms, zero or one oxygen atom, and zero or one sulfur atom;

The aromatic ring Ar^1 is substituted with -EAr^2 and the carboxamide group, C(=O)NHA, but no further substituents, and these substituents on Ar^1 are most preferably positioned in a 1,3-relationship relative to each other;

Ar^2 is substituted with zero or one substituents selected from: halogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, CN, NO_2, NR^1R^2, $CH_2NR^1R^2$, OR^3, CH_2OR^3, CO_2R^4, and CF_3; or an enantiomer thereof, and pharmaceutically acceptable salts thereof.

Particularly preferred embodiments of the invention include compounds of formula I wherein A represents:



II

D represents oxygen;

E represents oxygen, or NH;

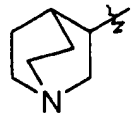
Ar^1 represents a 5- or 6-membered aromatic or heteroaromatic ring containing zero or one nitrogen atom, zero or one oxygen atom, and zero or one sulfur atom, and more preferably represents a benzene ring, furan ring or thiophene ring;

Ar^2 represents a 5- or 6-membered aromatic or heteroaromatic ring containing zero to three nitrogen atoms, zero or one oxygen atom, and zero or one sulfur atom;

The aromatic ring Ar^1 is substituted with $-EAr^2$ and the carboxamide group, C(=O)NHA, but no further substituents, and these substituents on Ar^1 are more preferably positioned in a 1,3-relationship relative to each other;

Ar^2 is substituted with zero or one substituents selected from: halogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, CN, NO_2, NR^1R^2, $CH_2NR^1R^2$, OR^3, CH_2OR^3, CO_2R^4, and CF_3; or an enantiomer thereof, and pharmaceutically acceptable salts thereof.

Preferred embodiments of the invention include compounds according to formula I wherein A represents:



II

and the configuration of the carbon atom in the quinuclidine to which the amide nitrogen is attached is (*R*), and pharmaceutically acceptable salts thereof.

Preferred compounds of the invention include the following:

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-phenylfuran-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-fluorophenyl)furan-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(3-thienyl)benzamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-phenylbenzamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(3-pyridyl)benzamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(3-methoxyphenyl)benzamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(2-methoxyphenyl)benzamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(3-(*N*-acetylamino)phenyl)benzamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(3-fluorophenyl)benzamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(3-methylphenyl)benzamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(2-thienyl)benzamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(3,5-dichlorophenyl)benzamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(2-naphthyl)benzamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(4-fluorophenyl)benzamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)furan-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-thienyl)furan-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-benzo[b]furanyl)furan-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)furan-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-thienyl)furan-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-methoxyphenyl)furan-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-methoxyphenyl)furan-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(4-fluorophenyl)furan-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-naphthyl)furan-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-methylphenyl)furan-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-furyl)furan-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-furyl)furan-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)furan-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)thiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(4-(2-pyridyl)thiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(4-(4-pyridyl)thiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(4-(3-pyridyl)thiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-acetylamino)phenyl)furan-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-nitrophenyl)furan-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-trifluoromethylphenyl)furan-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-chlorophenyl)furan-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-acetylamino)phenyl)thiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-fluorophenyl)thiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-methoxyphenyl)thiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-ethoxyphenyl)thiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3,5-dimethylisoxazol-4-yl)furan-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3,5-dimethylisoxazol-4-yl)thiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-aminophenyl)thiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-3-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(4-chlorophenyl)furan-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiazole-3-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiazole-3-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N,N*-dimethylamino)phenyl)thiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(8-quinolinyl)thiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-3-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(4-phenylthiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-cyanophenyl)thiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-methylamino)phenyl)thiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-hydroxyphenyl)thiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridylamino)thiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-chlorophenyl)thiophene-2-carboxamide);

N-(1-Aza-bicyclo[2.2.2]oct-3-yl)(5-(3-(4-morpholinyl)phenyl)thiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(aminomethyl)phenyl)thiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-phenoxythiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-aminophenyl)furan-2-carboxamide) ;

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N,N*-dimethylamino)phenyl)furan-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-formylphenyl)thiophene-2-carboxamide); and

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(hydroxymethyl)phenyl)thiophene-2-carboxamide).

Particularly preferred compounds of the invention include the following:

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-phenylfuran-2-carboxamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-fluorophenyl)furan-2-carboxamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(3-thienyl)benzamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-phenylbenzamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(3-pyridyl)benzamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-2-carboxamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(3-methoxyphenyl)benzamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(2-methoxyphenyl)benzamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(3-(*N*-acetylamino)phenyl)benzamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(3-fluorophenyl)benzamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(3-methylphenyl)benzamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(2-thienyl)benzamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(3,5-dichlorophenyl)benzamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(2-naphthyl)benzamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(4-fluorophenyl)benzamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)furan-2-carboxamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-thienyl)furan-2-carboxamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-benzo[b]furanyl)furan-2-carboxamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)furan-2-carboxamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-thienyl)furan-2-carboxamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-methoxyphenyl)furan-2-carboxamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-methoxyphenyl)furan-2-carboxamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(4-fluorophenyl)furan-2-carboxamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-naphthyl)furan-2-carboxamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-methylphenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-furyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-furyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(4-(2-pyridyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(4-(4-pyridyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(4-(3-pyridyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-acetylamino)phenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-nitrophenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-trifluoromethylphenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-chlorophenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-acetylamino)phenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-fluorophenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-methoxyphenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-ethoxyphenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3,5-dimethylisoxazol-4-yl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3,5-dimethylisoxazol-4-yl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-aminophenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-3-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)[5-(4-chlorophenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiazole-3-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiazole-3-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*,*N*-dimethylamino)phenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(8-quinolinyl)thiophene-2-carboxamide);

(S)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-2-carboxamide);

(S)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiophene-2-carboxamide);

(S)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)thiophene-2-carboxamide);

(S)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-3-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(4-phenylthiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-cyanophenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-methylamino)phenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)(5-(3-hydroxyphenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridylamino)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-chlorophenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Aza-bicyclo[2.2.2]oct-3-yl)(5-(3-(4-morpholinyl)phenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(aminomethyl)phenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-phenoxythiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-aminophenyl)furan-2-carboxamide) ;

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*,*N*-dimethylamino)phenyl)furan-2-carboxamide);

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-formylphenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(hydroxymethyl)phenyl)thiophene-2-carboxamide);

and pharmaceutically acceptable salts thereof.

Among these compounds, the following compounds of the invention are more particularly preferred:

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-phenylfuran-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-fluorophenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(3-thienyl)benzamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(3-phenylbenzamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(3-(*N*-acetylamino)phenyl)benzamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(2-thienyl)benzamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-thienyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-benzo[b]furanyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-thienyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-methoxyphenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(4-fluorophenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-naphthyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-methylphenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-furyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(4-(2-pyridyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-acetylamino)phenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-nitrophenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-trifluoromethylphenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-chlorophenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-acetylamino)phenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-fluorophenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-methoxyphenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-ethoxyphenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3,5-dimethylisoxazol-4-yl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-aminophenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-3-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)[5-(4-chlorophenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*,*N*-dimethylamino)phenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(8-quinolinyl)thiophene-2-carboxamide);

(S)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-2-carboxamide);

(S)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiophene-2-carboxamide);

(S)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)thiophene-2-carboxamide);

(S)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-3-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(4-phenylthiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-cyanophenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-methylamino)phenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-hydroxyphenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridylamino)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(4-morpholinyl)phenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(aminomethyl)phenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-phenoxythiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-aminophenyl)furan-2-carboxamide) ;

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*,*N*-dimethylamino)phenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(hydroxymethyl)phenyl)thiophene-2-carboxamide);

and pharmaceutically acceptable salts thereof.

Among these compounds, the following compounds of the invention are most particularly preferred:

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-fluorophenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-methoxyphenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(4-fluorophenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-acetylamino)phenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-nitrophenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-trifluoromethylphenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-chlorophenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-acetylamino)phenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-aminophenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-3-carboxamide);

(S)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-2-carboxamide);

(S)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(4-phenylthiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-cyanophenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-hydroxyphenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-phenoxythiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-aminophenyl)furan-2-carboxamide);

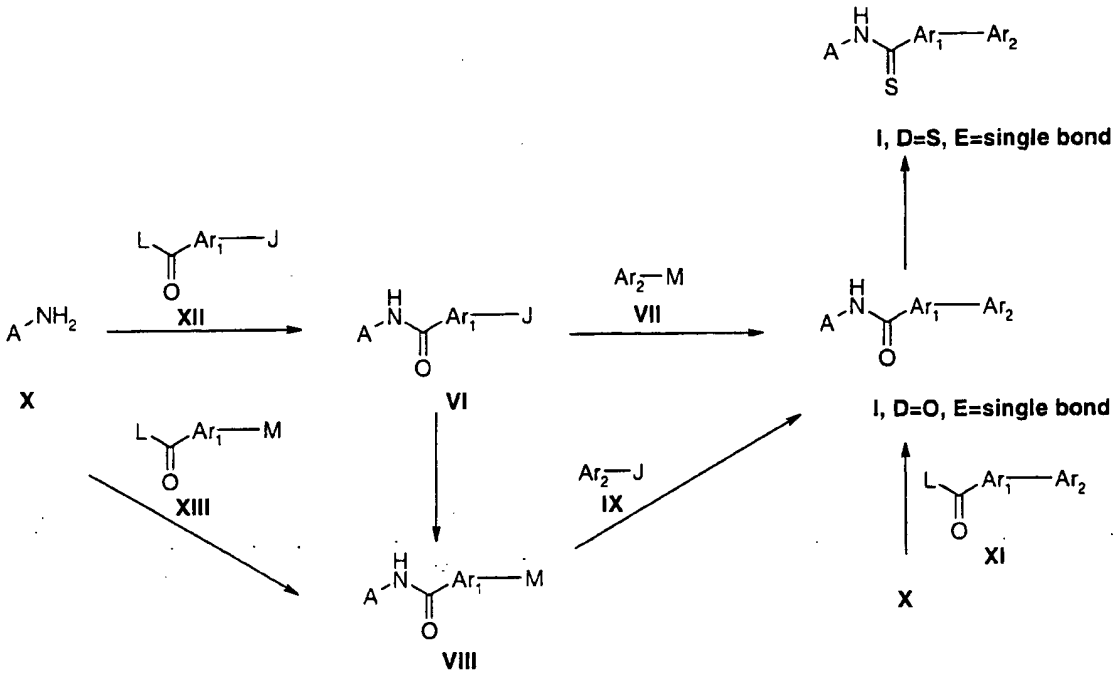
(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(hydroxymethyl)phenyl)thiophene-2-carboxamide);

and pharmaceutically acceptable salts thereof.

Methods of Preparation

In the reaction schemes and text that follow, A, E, Ar^1, and Ar^2 unless otherwise indicated, are as defined above for formula I.

The compounds of formula I in which E represent a single bond may be prepared according to the methods outlined in Scheme 1.



Scheme 1

Compounds of formula I wherein D represents oxygen and E represents a single bond may be prepared from compounds of formula VI wherein J represents a halogen or OSO_2CF_3 substituent at the position of ring Ar^1 at which the bond to ring Ar^2 is formed, by reaction with an appropriate organometallic compound of formula VII in the presence of a suitable organometallic catalyst and solvent. Suitable compounds of formula VII include boronic acids, in which M represents $B(OH)_2$ and organotin compounds, in which M represents a suitable trialkylstannyl group, for example trimethylstannyl or tri-n-butylstannyl. Suitable organometallic catalysts include palladium (0) complexes, for example tetrakis(triphenylphosphine)palladium(0) or a combination of tris(dibenzylideneacetone)dipalladium(0) and a suitable triarylphosphine or triarylarsine ligand, for example triphenylphosphine, tri(*o*-tolyl)phosphine or triphenylarsine. Suitable solvents include inert ether solvents, for example 1,2-dimethoxyethane, tetrahydrofuran, or 1,4-dioxane, or alcohols, such as ethanol, or mixtures thereof. If the compound of formula VII is a boronic acid, the presence of a suitable base in addition to the other reagents is preferred. Suitable bases include sodium carbonate, cesium carbonate, and barium hydroxide. The reaction is carried out at a temperature of 0-120 °C, and preferably at a temperature of 60-120 °C.

Compounds of formula I wherein D represents oxygen and E represents a single bond may also be prepared from organometallic compounds of formula VIII by reaction with a compound of formula IX in which J represents a halogen or OSO_2CF_3 in the presence of a suitable organometallic catalyst and solvent. Suitable compounds of formula VIII include boronic acids, in which M represents $B(OH)_2$ and organotin compounds, in which M represents a suitable trialkylstannyl group, for example trimethylstannyl or tri-n-butylstannyl. Suitable organometallic catalysts include palladium (0) complexes, for example tetrakis(triphenylphosphine)palladium (0) or a combination of tris(dibenzylideneacetone)dipalladium (0) and a suitable triarylphosphine or triarylarsine ligand, for example triphenylphosphine, tri(o-tolyl)phosphine or triphenylarsine. Suitable solvents include inert ether solvents, for example 1,2-dimethoxyethane, tetrahydrofuran, or 1,4-dioxane, or alcohols, such as ethanol, or mixtures thereof. If the compound of formula VIII is a boronic acid, the presence of a suitable base in addition to the other reagents is preferred. Suitable bases include sodium carbonate, cesium carbonate, and barium hydroxide. The reaction is carried out at a temperature of 0-120 °C, and preferably at a temperature of 60-120 °C.

Compounds of formula I wherein D represents oxygen and E represents a single bond may also be prepared from compounds of formula X by reaction with a suitable compound of formula XI, wherein L represents a suitable leaving group, using a suitable acylation procedure. Suitable leaving groups L include: OH, halogen, OAlkyl, OAryl, OCOAlkyl, OCOAryl. A suitable acylation procedure involves treatment of a compound of formula X with a compound of formula XI at 0-120 °C in a suitable solvent. The presence of a base, or, when Y=OH, a coupling agent, may also be necessary for the reaction to occur. Suitable bases for the reaction include: 4-(*N,N*-dimethylamino)pyridine, pyridine, triethylamine, *N,N*-diisopropylethylamine. The preferred base is *N,N*-diisopropylethylamine. Suitable coupling agents when L=OH include: carbodiimides, for example 1,3-dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl-3-ethylcarbodiimide hydrochloride; phosphonium reagents, for example benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate or benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate; and uronium reagents, for example *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate. The preferred coupling agent is O-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate. Suitable solvents for the reaction include *N,N*-dimethylformamide, dimethylsulfoxide,

tetrahydrofuran, or chloroform. The preferred solvent is *N,N*-dimethylformamide. The reaction is preferably performed at a temperature of 0-50 °C, and most preferably at a temperature of 20-30 °C.

Compounds of formula I in which D represents sulfur and E represents a single bond may be prepared from compounds of formula I in which D represents oxygen and E represents a single bond by reaction with a suitable sulfide in a suitable solvent. The preferred sulfides are phosphorus sulfides, in particular 4-methoxyphenylthionophosphine sulfide dimer ("Lawesson's Reagent"), and diphosphorus pentasulfide. Suitable solvents for the reaction include aryl hydrocarbon solvents, for example toluene or xylene. The reaction is performed at a temperature of 0-200 °C, and preferably at a temperature of 50-180 °C.

Certain compounds of formula VI wherein J represents halogen may be prepared from compounds of formula VI wherein J represents hydrogen by reaction with a suitable halogenating agent in a suitable solvent. Suitable halogenating agents include bromine. Suitable solvents include acetic acid. The reaction is preferably performed at a temperature of 0-50 °C, and most preferably at a temperature of 0-25 °C.

Compounds of formula VI wherein J represents OSO_2CF_3 may be prepared from compounds of formula VI wherein J represents OH by reaction with trifluoromethanesulfonic anhydride or other trifluoromethanesulfonylating agent in the presence of a base and a suitable solvent. Suitable bases include pyridine, and 2,6-di-t-butylpyridine. The reaction is preferably performed at a temperature of -78 to 120 °C, and most preferably at a temperature of -78 to 0 °C.

Compounds of formula VI wherein J represents hydrogen, halogen, OH, or OSO_2CF_3 may be prepared from compounds of formula X by reaction with a suitable compound of formula XII, wherein L represents a suitable leaving group and J represents hydrogen, halogen, OH, or OSO_2CF_3, using a suitable acylation procedure. Suitable leaving groups L include: OH, halogen, OAlkyl, OAryl, OCOAlkyl, OCOAryl. A suitable acylation procedure involves treatment of a compound of formula X with a compound of formula XII at 0-120 °C in a suitable solvent. The presence of a base, or, when L=OH, a coupling agent, may also be necessary for the reaction to occur. Suitable bases for the reaction include: 4-(*N,N*-dimethylamino)pyridine, pyridine, triethylamine, *N,N*-diisopropylethylamine. The preferred base is *N,N*-diisopropylethylamine. Suitable coupling agents when Y=OH include: carbodiimides, for example 1,3-dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl-3-ethylcarbodiimide hydrochloride; phosphonium reagents, for

example benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate or benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate; and uronium reagents, for example *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate. The preferred coupling agent is *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate. Suitable solvents for the reaction include *N,N*-dimethylformamide, dimethylsulfoxide, tetrahydrofuran, or chloroform. The preferred solvent is *N,N*-dimethylformamide. The reaction is preferably performed at a temperature of 0-50 °C, and most preferably at a temperature of 20-30 °C.

Compounds of formula VIII in which M represents $B(OH)_2$ may be prepared from compounds of formula VI in which J represents hydrogen, halogen, or OSO_2CF_3 by methods known to one skilled in the art. For example compounds of formula VI in which J represents hydrogen or halogen may be converted to compounds of formula VIII in which M represents $B(OH)_2$ via conversion to the corresponding aryllithium or arylmagnesium compounds followed by reaction with trimethylborate and subsequent hydrolysis of the resulting borate ester. The reaction is performed in a suitable inert solvent, for example, tetrahydrofuran. Alternatively, compounds of formula VI wherein J represents halogen or OSO_2CF_3 may be converted to compounds of formula VIII in which M represents $B(OH)_2$ *via* reaction with bis(pinacolato)diboron and an organometallic catalyst, followed by hydrolysis of the resulting borate ester. For typical procedures for effecting such conversions, see, for example, *Organic Syntheses*, **1963**, *Coll. Vol. 4*, 68; *J. Org. Chem.* **1995**, *60*, 7508.

Compounds of formula VIII in which M represents a trialkylstannyl group may be prepared from compounds of formula VI in which J represents hydrogen, halogen, or OSO_2CF_3 by methods known to one skilled in the art. For example compounds of formula VI in which J represents hydrogen or halogen may be converted to compounds of formula VIII in which M represents a trialkylstannyl group via conversion to the corresponding aryllithium or arylmagnesium compounds followed by reaction with an appropriate trialkylstannyl halide. The reaction is performed in a suitable inert solvent, for example, tetrahydrofuran. The reaction is performed at a temperature of -78 °C to 20 °C, preferably at -78 °C to 0 °C. Alternatively, compounds of formula VI wherein J represents halogen or OSO_2CF_3 may be converted to compounds of formula VIII in which M represents a trialkylstannyl group *via* reaction with the appropriate bis(trialkyltin). The reaction is performed in a suitable inert solvent, for example tetrahydrofuran, in the presence of a

suitable organometallic catalyst, for example tetrakis(triphenylphosphine). The reaction is performed at a temperature of 0 °C to 150 °C, preferably at 20 °C to 100 °C.

Compounds of formula VIII wherein M represents $B(OH)_2$ or a trialkylstannyl group may be prepared from compounds of formula X by reaction with a suitable compound of formula XIII, wherein L represents a suitable leaving group M represents $B(OH)_2$ or a trialkylstannyl group, using a suitable acylation procedure. Suitable leaving groups L include: OH, halogen, OAlkyl, OAryl, OCOAlkyl, OCOAryl. A suitable acylation procedure involves treatment of a compound of formula X with a compound of formula XIII at 0-120 °C in a suitable solvent. The presence of a base, or, when L=OH, a coupling agent, may also be necessary for the reaction to occur. Suitable bases for the reaction include: 4-(*N,N*-dimethylamino)pyridine, pyridine, triethylamine, *N,N*-diisopropylethylamine. The preferred base is *N,N*-diisopropylethylamine. Suitable coupling agents when L=OH include: carbodiimides, for example 1,3-dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl-3-ethylcarbodiimide hydrochloride; phosphonium reagents, for example benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate or benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate; and uronium reagents, for example *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate. The preferred coupling agent is *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate. Suitable solvents for the reaction include *N,N*-dimethylformamide, dimethylsulfoxide, tetrahydrofuran, or chloroform. The preferred solvent is *N,N*-dimethylformamide. The reaction is preferably performed at a temperature of 0-50 °C, and most preferably at a temperature of 20-30 °C.

Compounds of formula XI may be prepared from compounds of formula XII wherein J represents a halogen or OSO_2CF_3 substituent at the position of ring Ar^1 at which the bond to ring Ar^2 is formed, by reaction with an appropriate organometallic compound of formula VII in the presence of a suitable organometallic catalyst and solvent. Suitable compounds of formula VII include boronic acids, in which M represents $B(OH)_2$ and organotin compounds, in which M represents a suitable trialkylstannyl group, for example trimethylstannyl or tri-n-butylstannyl. Suitable organometallic catalysts include palladium (0) complexes, for example tetrakis(triphenylphosphine)palladium (0) or a combination of tris(dibenzylidieneacetone)dipalladium (0) and a suitable triarylphosphine or triarylarsine ligand, for example triphenylphosphine, tri(o-tolyl)phosphine or triphenylarsine. Suitable solvents include inert ether solvents, for example 1,2-dimethoxyethane, tetrahydrofuran, or

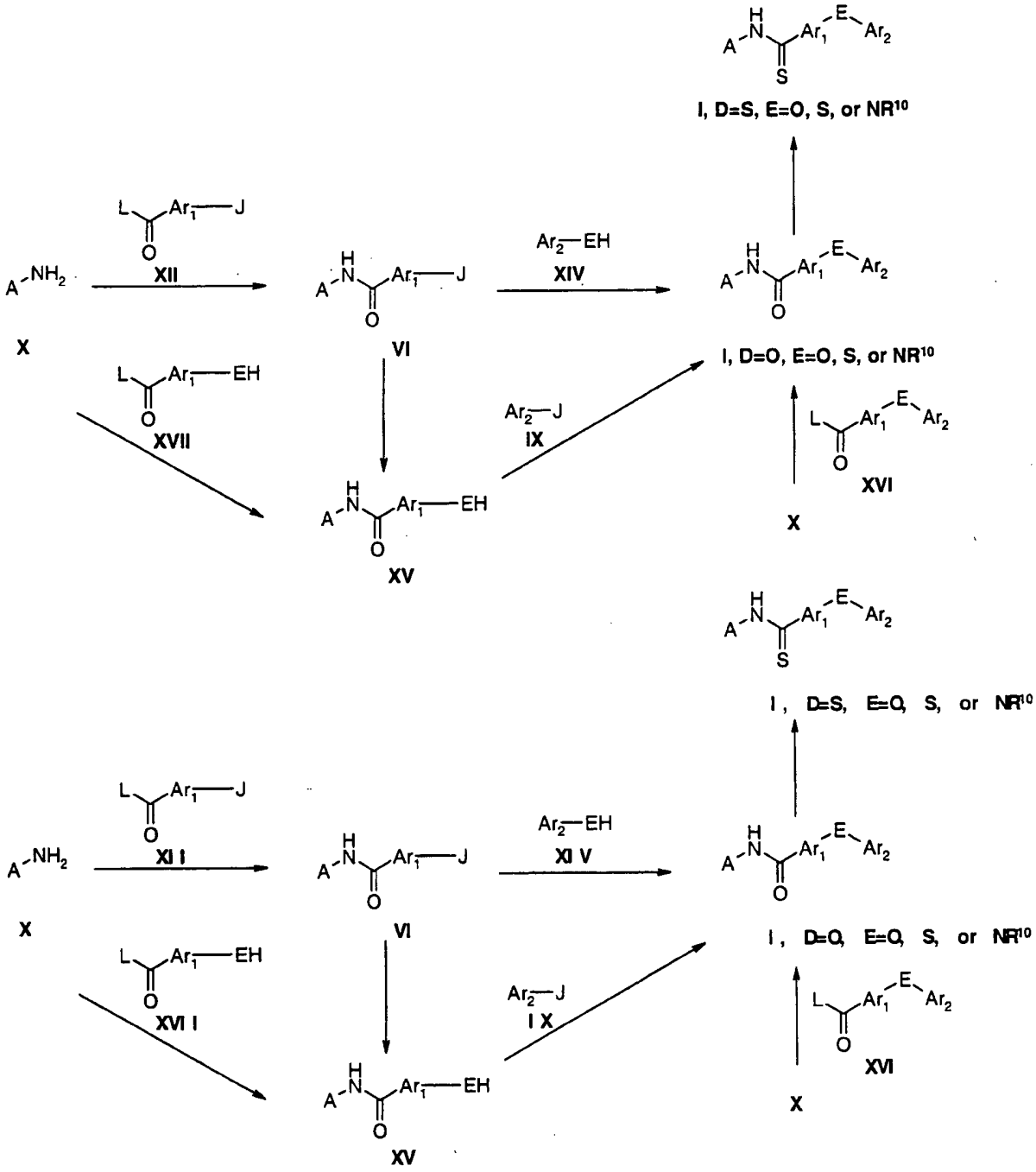
1,4-dioxane, or alcohols, such as ethanol, or mixtures thereof. If the compound of formula VII is a boronic acid, the presence of a suitable base in addition to the other reagents is preferred. Suitable bases include sodium carbonate, cesium carbonate, and barium hydroxide. The reaction is carried out at a temperature of 0-120 °C, and preferably at a temperature of 60-120 °C.

Compounds of formula XI may also be prepared from organometallic compounds of formula XIII by reaction with a compound of formula IX in which J represents a halogen or OSO_2CF_3 in the presence of a suitable organometallic catalyst and solvent. Suitable compounds of formula XIII include boronic acids, in which M represents $B(OH)_2$ and organotin compounds, in which M represents a suitable trialkylstannyl group, for example trimethylstannyl or tri-n-butylstannyl. Suitable organometallic catalysts include palladium (0) complexes, for example tetrakis(triphenylphosphine)palladium (0) or a combination of tris(dibenzylideneacetone)dipalladium (0) and a suitable triarylphosphine or triarylarsine ligand, for example triphenylphosphine, tri(o-tolyl)phosphine or triphenylarsine. Suitable solvents include inert ether solvents, for example 1,2-dimethoxyethane, tetrahydrofuran, or 1,4-dioxane, or alcohols, such as ethanol, or mixtures thereof. If the compound of formula VIII is a boronic acid, the presence of a suitable base in addition to the other reagents is preferred. Suitable bases include sodium carbonate, cesium carbonate, and barium hydroxide. The reaction is carried out at a temperature of 0-120 °C, and preferably at a temperature of 60-120 °C.

Compounds of formula VII and compounds of formula XIII are either commercially available, or may be prepared by methods known to one skilled in the art. In particular, methods are known to one skilled in the art for the conversion of aryl halides or heteroaryl halides to aryl or heteroaryl boronic acids or aryl or heteroaryl trialkylstannanes, providing methods for the conversion of compounds of formula IX in which J represents halogen to compounds of formula VII and compounds of formula XII in which J represents halogen to compounds of formula XIII. For example, boronic acids may be synthesised from aryl or heteroaryl halides via conversion to the aryllithium or arylmagnesium compounds followed by reaction with trimethylborate, or *via* reaction with bis(pinacolato)diboron and an organometallic catalyst, followed by hydrolysis of the resulting borate ester (see, for example, *Organic Syntheses*, **1963**, *Coll. Vol. 4*, 68; *J. Org. Chem.* **1995**, *60*, 7508). Trialkylstannanes may be synthesised from aryl or heteroaryl halides *via* conversion to the aryllithium or arylmagnesium compounds followed by reaction with the appropriate

chlorotrialkyltin, or *via* reaction with the appropriate bis(trialkyltin) and an organometallic catalyst.

The compounds of formula I in which E represents oxygen, sulfur, or NR^{10} may be prepared according to the methods outlined in Scheme 2.



Scheme 2

Compounds of formula I wherein D represents oxygen and E represents NR^{10} may be prepared from compounds of formula VI wherein J represents a halogen or OSO_2CF_3 substituent at the position of ring Ar^1 at which the bond to nitrogen is formed, by reaction with an appropriate amine of formula XIV in which EH represents NHR^{10}. The reaction may be performed by heating in an inert solvent in the presence of a suitable strong base. Suitable inert solvents include ether solvents, for example tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane, or di(2-methoxyethyl)ether, a hydrocarbon solvent, for example benzene or toluene, or an amide solvent, for example dimethylformamide, or *N*-methyl-2-pyrrolidinone. The preferred solvent is tetrahydrofuran. Suitable strong bases include alkali metal alkoxide or amide bases, for example sodium t-butoxide or potassium t-butoxide, lithium bis(trimethylsilyl)amide, or lithium diisopropylamide. The preferred strong base is sodium t-butoxide. The reaction may require, and is preferably performed in, the presence of an organometallic catalyst. Suitable organometallic catalysts include complexes of palladium (0) with a suitable phosphine ligand, preferably a triarylphosphine ligand, and most preferably a bidentate triarylphosphine ligand. Preferred ligands include 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl or 1,1'-bis(diphenylphosphino)ferrocene. The catalyst may be synthesised by the combination of a suitable source of palladium (0), for example tris(dibenzylideneacetone)dipalladium (0), with the phosphine ligand, and may either be pre-formed or formed in situ by including the palladium source and phophine ligand in the reaction mixture. The reaction is carried out at a temperature of 0-150 °C, and preferably at a temperature of 60-120 °C.

Compounds of formula I wherein D represents oxygen and E represents NR^{10} may also be prepared from compounds of formula IX wherein J represents a halogen or OSO_2CF_3 substituent at the position of ring Ar^2 at which the bond to nitrogen is formed, by reaction with an appropriate amine of formula XV in which EH represents NHR^{10}. The reaction may be performed by heating in an inert solvent in the presence of a suitable strong base. Suitable inert solvents include ether solvents, for example tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane, or di(2-methoxyethyl)ether, a hydrocarbon solvent, for example benzene or toluene, or an amide solvent, for example dimethylformamide, or *N*-methyl-2-pyrrolidinone. The preferred solvent is tetrahydrofuran. Suitable strong bases include alkali metal alkoxide or amide bases, for example sodium *t*-butoxide or potassium t-butoxide, lithium bis(trimethylsilyl)amide, or lithium diisopropylamide. The preferred strong base is sodium t-butoxide. The reaction may require, and is preferably performed in,

the presence of an organometallic catalyst. Suitable organometallic catalysts include complexes of palladium (0) with a suitable phosphine ligand, preferably a triarylphosphine ligand, and most preferably a bidentate triarylphosphine ligand. Preferred ligands include 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl or 1,1'-bis(diphenylphosphino)ferrocene. The catalyst may be synthesised by the combination of a suitable source of palladium (0), for example tris(dibenzylideneacetone)dipalladium (0), with the phosphine ligand, and may either be pre-formed or formed in situ by including the palladium source and phophine ligand in the reaction mixture. The reaction is carried out at a temperature of 0-150 °C, and preferably at a temperature of 60-120 °C.

Compounds of formula I wherein D represents oxygen and E represents oxygen or sulfur may be prepared from compounds of formula VI wherein J represents a halogen or OSO_2CF_3 substituent at the position of ring Ar^1 at which the bond to oxygen is formed, by reaction with an appropriate compound of formula XIV in which EH represents OH or SH. The reaction may be performed by heating in an inert solvent in the presence of a suitable base. The reaction may require, and is preferably performed in, the presence of a catalyst. Suitable inert solvents include ether solvents, for example tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane, or di(2-methoxyethyl)ether, an amide solvent, for example dimethylformamide, or *N*-methyl-2-pyrrolidinone, or a basic heterocyclic aromatic solvent, for example pyridine. The preferred solvent is pyridine. Suitable bases include alkali metal alkoxides, or alkali metal carbonates, for example potassium carbonate. Suitable organometallic catalysts include copper or its salts, preferably copper (I) salts, and most preferably copper (I) iodide. The reaction is carried out at a temperature of 0-150 °C, and preferably at a temperature of 100-150 °C.

Compounds of formula I wherein D represents oxygen and E represents oxygen or sulfur may also be prepared from compounds of formula IX wherein J represents a halogen or OSO_2CF_3 substituent at the position of ring Ar^2 at which the bond to nitrogen is formed, by reaction with an appropriate compound of formula XV in which EH represents OH or SH. The reaction may be performed by heating in an inert solvent in the presence of a suitable base. The reaction may require, and is preferably performed in, the presence of a catalyst. Suitable inert solvents include ether solvents, for example tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane, or di(2-methoxyethyl)ether, an amide solvent, for example *N,N*-dimethylformamide, or *N*-methylpyrrolidinone, or a basic heterocyclic aromatic solvent, for example pyridine. The preferred solvent is pyridine. Suitable bases include

alkali metal alkoxides, or alkali metal carbonates, for example potassium carbonate. Suitable organometallic catalysts include copper or its salts, preferably copper (I) salts, and most preferably copper (I) iodide. The reaction is carried out at a temperature of 0-150 °C, and preferably at a temperature of 100-150 °C.

Compounds of formula I wherein D represents oxygen and E represents oxygen, sulfur, or NR^{10} may also be prepared from compounds of formula X by reaction with a suitable compound of formula XVI, wherein E represents oxygen, sulfur, or NR^{10} and L represents a suitable leaving group, using a suitable acylation procedure. Suitable leaving groups L include: OH, halogen, OAlkyl, OAryl, OCOAlkyl, OCOAryl. A suitable acylation procedure involves treatment of a compound of formula X with a compound of formula XI at 0-120 °C in a suitable solvent. The presence of a base, or, when Y=OH, a coupling agent, may also be necessary for the reaction to occur. Suitable bases for the reaction include: 4-(*N,N*-dimethylamino)pyridine, pyridine, triethylamine, *N,N*-diisopropylethylamine. The preferred base is *N,N*-diisopropylethylamine. Suitable coupling agents when L=OH include: carbodiimides, for example 1,3-dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl-3-ethylcarbodiimide hydrochloride; phosphonium reagents, for example benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate or benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate; and uronium reagents, for example *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate. The preferred coupling agent is O-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate. Suitable solvents for the reaction include *N,N*-dimethylformamide, dimethylsulfoxide, tetrahydrofuran, or chloroform. The preferred solvent is *N,N*-dimethylformamide. The reaction is preferably performed at a temperature of 0-50 °C, and most preferably at a temperature of 20-30 °C.

Compounds of formula XV wherein EH represents OH, SH, or NHR^{10} may be prepared from compounds of formula X by reaction with a suitable compound of formula XVII, wherein L represents a suitable leaving group and EH represents OH, SH or NHR^{10}, using a suitable acylation procedure. Suitable leaving groups L include: OH, halogen, OAlkyl, OAryl, OCOAlkyl, OCOAryl. A suitable acylation procedure involves treatment of a compound of formula X with a compound of formula XVII at 0-120 °C in a suitable solvent. The presence of a base, or, when L=OH, a coupling agent, may also be necessary for the reaction to occur. Suitable bases for the reaction include: 4-(*N,N*-dimethylamino)pyridine, pyridine, triethylamine, *N,N*-diisopropylethylamine. The preferred

base is *N,N*-diisopropylethylamine. Suitable coupling agents when L=OH include: carbodiimides, for example 1,3-dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl-3-ethylcarbodiimide hydrochloride; phosphonium reagents, for example benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate or benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate; and uronium reagents, for example *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate. The preferred coupling agent is *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate. Suitable solvents for the reaction include *N,N*-dimethylformamide, dimethylsulfoxide, tetrahydrofuran, or chloroform. The preferred solvent is *N,N*-dimethylformamide. The reaction is preferably performed at a temperature of 0-50 °C, and most preferably at a temperature of 20-30 °C.

Compounds of formula I, XIV, XV or XVII in which E represents NR^{10} and R^{10} represents an alkyl group may be prepared from compounds of the corresponding formula wherein R^{10} represents hydrogen by a suitable alkylation procedure. Typical alkylation procedures include treatment with an appropriate alkyl halide or sulfonate ester and base, for example sodium hydride, in a suitable solvent, for example *N,N*-dimethylformamide, or reductive alkylation using the appropriate aldehyde or ketone together with a suitable reducing agent in the presence of an acidic catalyst and in an inert solvent. The preferred method is reductive alkylation. Suitable reducing agents include sodium borohydride and sodium cyanoborohydride. The preferred reducing agent is sodium borohydride. Suitable inert solvents include water, methanol or ethanol. The preferred solvent is methanol. Suitable acidic catalysts include acetic acid or zinc chloride. The preferred acidic catalyst is acetic acid. The reaction is usually conducted at a temperature of 0-100 °C, and preferably at 20-65 °C.

Compounds of formula I, XIV, XV or XVII in which E represents NR^{10} and R^{10} represents an aryl or heteroaryl group may be prepared from compounds of the corresponding formula wherein R^{10} represents hydrogen by reaction with an appropriate aromatic or heteroaromatic halide or trifluoromethanesulfonate. The reaction may be performed by heating in an inert solvent in the presence of a suitable strong base. Suitable inert solvents include ether solvents, for example tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane, or di(2-methoxyethyl)ether, a hydrocarbon solvent, for example benzene or toluene, or an amide solvent, for example *N,N*-dimethylformamide, or *N*-methyl-2-pyrrolidinone. The preferred solvent is tetrahydrofuran. Suitable strong bases include

alkali metal alkoxide or amide bases, for example sodium t-butoxide or potassium t-butoxide, lithium bis(trimethylsilyl)amide, or lithium diisopropylamide. The preferred strong base is sodium t-butoxide. The reaction may require, and is preferably performed in, the presence of an organometallic catalyst. Suitable organometallic catalysts include complexes of palladium (0) with a suitable phosphine ligand, preferably a triarylphosphine ligand, and most preferably a bidentate triarylphosphine ligand. Preferred ligands include 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl or 1,1'-bis(diphenylphosphino)ferrocene. The catalyst may be synthesised by the combination of a suitable source of palladium (0), for example tris(dibenzylidieneacetone)dipalladium (0), with the phosphine ligand, and may either be preformed or formed in situ by including the palladium source and phophine ligand in the reaction mixture. The reaction is carried out at a temperature of 0-150 °C, and preferably at a temperature of 60-120 °C.

Compounds of formula I in which D represents sulfur and E represents oxygen or NR^{10} may be prepared from compounds of formula I in which D represents oxygen and E represents oxygen, or NR^{10} by reaction with a suitable sulfide in a suitable solvent. The preferred sulfides are phosphorus sulfides, in particular 4-methoxyphenylthionophosphine sulfide dimer ("Lawesson's Reagent"), and diphosphorus pentasulfide. Suitable solvents for the reaction include aryl hydrocarbon solvents, for example toluene or xylene. The reaction is performed at a temperature of 0-200 °C, and preferably at a temperature of 50-180 °C.

Compounds of formula XVI wherein D represents oxygen and E represents NR^{10} may be prepared from compounds of formula XII wherein J represents a halogen or OSO_2CF_3 substituent at the position of ring Ar^1 at which the bond to nitrogen is formed, by reaction with an appropriate amine of formula XIV in which EH represents NHR^{10}, or, alternatively, from compounds of formula XVII in which EH represents NHR^{10} by reaction with an appropriate compound of formula IX wherein J represents a halogen or OSO_2CF_3 substituent at the position of ring Ar^2 at which the bond to nitrogen is formed. The reaction may be performed by heating in an inert solvent in the presence of a suitable strong base. Suitable inert solvents include ether solvents, for example tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane, or di(2-methoxyethyl)ether, a hydrocarbon solvent, for example benzene or toluene, or an amide solvent, for example *N,N*-dimethylformamide, or *N*-methyl-2-pyrrolidinone. The preferred solvent is tetrahydrofuran. Suitable strong bases include alkali metal alkoxide or amide bases, for example sodium t-butoxide or potassium t-butoxide, lithium bis(trimethylsilyl)amide, or lithium diisopropylamide. The preferred

strong base is sodium t-butoxide. The reaction may require, and is preferably performed in, the presence of an organometallic catalyst. Suitable organometallic catalysts include complexes of palladium (0) with a suitable phosphine ligand, preferably a triarylphosphine ligand, and most preferably a bidentate triarylphosphine ligand. Preferred ligands include 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl or 1,1'-bis(diphenylphosphino)ferrocene. The catalyst may be synthesised by the combination of a suitable source of palladium (0), for example tris(dibenzylideneacetone)dipalladium (0), with the phosphine ligand, and may either be pre-formed or formed in situ by including the palladium source and phophine ligand in the reaction mixture. The reaction is carried out at a temperature of 0-150 °C, and preferably at a temperature of 60-120 °C.

Compounds of formula XVI wherein D represents oxygen and E represents oxygen or sulfur may be prepared from compounds of formula XII wherein J represents a halogen or OSO_2CF_3 substituent at the position of ring Ar^1 at which the bond to oxygen or sulfur is formed, by reaction with an appropriate compound of formula XIV in which EH represents OH or SH, or, alternatively, from compounds of formula XVII in which EH represents OH or SH by reaction with an appropriate compound of formula IX wherein J represents a halogen or OSO_2CF_3 substituent at the position of ring Ar^2 at which the bond to oxygen or sulfur is formed. The reaction may be performed by heating in an inert solvent in the presence of a suitable base. The reaction may require, and is preferably performed in, the presence of a catalyst. Suitable inert solvents include ether solvents, for example tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane, or di(2-methoxyethyl)ether, an amide solvent, for example *N,N*-dimethylformamide, or *N*-methyl-2-pyrrolidinone, or a basic heterocyclic aromatic solvent, for example pyridine. The preferred solvent is pyridine. Suitable bases include alkali metal alkoxides, or alkali metal carbonates, for example potassium carbonate. Suitable organometallic catalysts include copper or its salts, preferably copper (I) salts, and most preferably copper (I) iodide. The reaction is carried out at a temperature of 0-150 °C, and preferably at a temperature of 100-150 °C.

Compounds of formula IX, X, and XII, XIV, and XVII are either commercially available, known in the literature, or may be prepared by methods known to one skilled in the art.

It will be appreciated by one skilled in the art that certain optional aromatic substituents in the compounds of the invention may be introduced by employing aromatic substitution reactions, or functional group transformations to modify an existing

substituent, or a combination thereof. Such reactions may be effected either prior to or immediately following the processes mentioned above, and are included as part of the process aspect of the invention. The reagents and reaction conditions for such procedures are known in the art. Specific examples of procedures which may be employed include, but are not limited to, electrophilic functionalisation of an aromatic ring, for example via nitration, halogenation, or acylation; transformation of a nitro group to an amino group, for example via reduction, such as by catalytic hydrogenation; acylation, alkylation, sulfonylation of an amino or hydroxyl group; replacement of an amino group by another functional group via conversion to an intermediate diazonium salt followed by nucleophilic or free radical substitution of the diazonium salt; or replacement of a halogen by another functional group, for example via nucleophilic or organometallically-catalysed substitution reactions.

Where necessary, hydroxy, amino, or other reactive groups may be protected using a protecting group as described in the standard text "Protecting groups in Organic Synthesis", 3rd Edition (1999) by Greene and Wuts.

The above described reactions, unless otherwise noted, are usually conducted at a pressure of about one to about three atmospheres, preferably at ambient pressure (about one atmosphere).

Unless otherwise stated, the above described reactions are conducted under an inert atmosphere, preferably under a nitrogen atmosphere.

The compounds of the invention and intermediates may be isolated from their reaction mixtures by standard techniques.

Acid addition salts of the compounds of formula I which may be mentioned include salts of mineral acids, for example the hydrochloride and hydrobromide salts; and salts formed with organic acids such as formate, acetate, maleate, benzoate, tartrate, and fumarate salts.

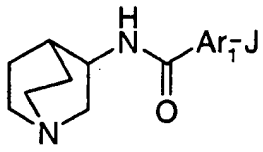
Acid addition salts of compounds of formula I may be formed by reacting the free base or a salt, enantiomer or protected derivative thereof, with one or more equivalents of the appropriate acid. The reaction may be carried out in a solvent or medium in which the salt is insoluble or in a solvent in which the salt is soluble, e.g., water, dioxane, ethanol, tetrahydrofuran or diethyl ether, or a mixture of solvents, which may be removed in vacuum or by freeze drying. The reaction may be a metathetical process or it may be carried out on an ion exchange resin.

The compounds of formula I exist in tautomeric or enantiomeric forms, all of which are included within the scope of the invention. The various optical isomers may be isolated by separation of a racemic mixture of the compounds using conventional techniques, e.g. fractional crystallisation, or chiral HPLC. Alternatively the individual enantiomers may be made by reaction of the appropriate optically active starting materials under reaction conditions which will not cause racemisation.

Intermediates

A further aspect of the invention relates to intermediates. Of interest among the intermediates are compounds of formula VI in Scheme 1. These intermediates are useful in the synthesis of compounds of formula I, but their use is not limited to the synthesis of such compounds. For example, compounds of formula VI are active as ligands for acetylcholine receptors, and therefore share the utilities described for compounds of formula I.

Accordingly, there is also provided a compound of formula VI:



VI

wherein:

Ar^1 represents a benzene, furan, or thiophene ring;

J represents halogen, or OSO_2CF_3, provided that when Ar^1 represents a benzene ring, J may only represent bromine, iodine, or OSO_2CF_3 in a position meta or para to the carboxamide group; or an enantiomer thereof and pharmaceutically acceptable salts thereof.

Preferred compounds of this aspect of the invention include the following:

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-bromofuran-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-bromothiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-bromobenzamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(4-bromobenzamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-iodobenzamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(4-iodobenzamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(4-bromothiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-bromothiophene-3-carboxamide);

or an enantiomer thereof, and pharmaceutically acceptable salts thereof.

Particularly preferred compounds of this aspect of the invention include the following:

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-bromofuran-2-carboxamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-bromothiophene-2-carboxamide);

(S)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-bromothiophene-2-carboxamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-bromobenzamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(4-bromobenzamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-iodobenzamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(4-iodobenzamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(4-bromothiophene-2-carboxamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-bromothiophene-3-carboxamide);

or an enantiomer thereof, and pharmaceutically acceptable salts thereof.

Intermediate compounds also exist in enantiomeric forms and may be used as purified enantiomers, racemates or mixtures.

Pharmaceutical Compositions

A further aspect of the invention relates to a pharmaceutical composition for treating or preventing a condition or disorder as exemplified below arising from dysfunction of nicotinic acetylcholine receptor neurotransmission in a mammal, preferably a human, comprising an amount of a compound of formula I, an enantiomer thereof or a pharmaceutically acceptable salt thereof, effective in treating or preventing such disorder or condition in admixture with an inert pharmaceutically acceptable diluent or carrier.

For the above-mentioned uses the dosage administered will, of course, vary with the compound employed, the mode of administration and the treatment desired. However, in general, satisfactory results are obtained when the compounds of the invention are administered at a daily dosage of from about 0.1 mg to about 20 mg per kg of animal body weight, preferably given in divided doses 1 to 4 times a day or in sustained release form. For man, the total daily dose is in the range of from 5 mg to 1,400 mg, more preferably from 10 mg to 100 mg, and unit dosage forms suitable for oral administration comprise

from 2 mg to 1,400 mg of the compound admixed with a solid or liquid pharmaceutical carrier or diluent.

The compounds of formula I, or an enantiomer thereof, and pharmaceutically acceptable salts thereof, may be used on their own or in the form of appropriate medicinal preparations for enteral or parenteral administration. According to a further aspect of the invention, there is provided a pharmaceutical composition including preferably less than 80% and more preferably less than 50% by weight of a compound of the invention in admixture with an inert pharmaceutically acceptable diluent or carrier.

Examples of diluents and carriers are:

– for tablets and dragees: lactose, starch, talc, stearic acid; for capsules: tartaric acid or lactose;

– for injectable solutions: water, alcohols, glycerin, vegetable oils; for suppositories: natural or hardened oils or waxes.

There is also provided a process for the preparation of such a pharmaceutical composition which comprises mixing the ingredients.

Utility

A further aspect of the invention is the use of a compound according to the invention, an enantiomer thereof or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of one of the below mentioned diseases or conditions; and a method of treatment or prophylaxis of one of the above mentioned diseases or conditions, which comprises administering a therapeutically effective amount of a compound according to the invention, or an enantiomer thereof or a pharmaceutically acceptable salt thereof, to a patient.

Compounds according to the invention are agonists of nicotinic acetylcholine receptors. While not being limited by theory, it is believed that agonists of the α_7 nAChR (nicotinic acetylcholine receptor) subtype should be useful in the treatment or prophylaxis of psychotic disorders and intellectual impairment disorders, and have advantages over compounds which are or are also agonists of the α_4 nAChR subtype. Therefore, compounds which are selective for the α_7 nAChR subtype are preferred. The compounds of the invention are indicated as pharmaceuticals, in particular in the treatment or prophylaxis of psychotic disorders and intellectual impairment disorders. Examples of psychotic disorders include schizophrenia, mania and manic depression, and anxiety. Examples of intellectual

impairment disorders include Alzheimer's disease, learning deficit, cognition deficit, attention deficit, Lewy Body Dementia, memory loss, and Attention Deficit Hyperactivity Disorder. The compounds of the invention may also be useful as analgesics in the treatment of pain (including chronic pain) and in the treatment or prophylaxis of Parkinson's disease, Huntington's disease, Tourette's syndrome, and neurodegenerative disorders in which there is loss of cholinergic synapses. The compounds may further be indicated for the treatment or prophylaxis of jetlag, for use in inducing the cessation of smoking, and for the treatment or prophylaxis of nicotine addiction (including that resulting from exposure to products containing nicotine).

It is also believed that compounds according to the invention are useful in the treatment and prophylaxis of ulcerative colitis.

Pharmacology

The pharmacological activity of the compounds of the invention may be measured in the tests set out below:

Test A - Assay for affinity at α_7 nAChR subtype

^{125}I-α -Bungarotoxin (BTX) binding to rat hippocampal membranes. Rat hippocampi were homogenized in 20 volumes of cold homogenisation buffer (HB: concentrations of constituents (mM): tris(hydroxymethyl)aminomethane 50; $MgCl_2$ 1; NaCl 120; KCl 5: pH 7.4). The homogenate was centrifuged for 5 minutes at 1000 g, the supernatant was saved and the pellet re-extracted. The pooled supernatants were centrifuged for 20 minutes at 12000 g, washed, and re-suspended in HB. Membranes (30–80 µg) were incubated with 5 nM [^{125}I] α -BTX, 1 mg/mL BSA (bovine serum albumin), test drug, and either 2 mM $CaCl_2$ or 0.5 mM EGTA [ethylene glycol-bis(β -aminoethylether)] for 2 hours at 21° C, and then filtered and washed 4 times over Whatman glass fibre filters (thickness C) using a Brandel cell harvester. Pre-treating the filters for 3 hours with 1% (BSA/0.01% PEI (polyethyleneimine) in water was critical for low filter blanks (0.07% of total counts per minute). Non-specific binding was described by 100 µ M (–)-nicotine, and specific binding was typically 75%.

Test B - Assay for affinity to the α_4 nAChR subtype

[^{3}H] -(–)-nicotine binding. Using a procedure modified from Martino-Barrows and Kellar (Mol Pharm (1987) 31:169-174), rat brain (cortex and hippocampus) was homogenised as in the [^{125}I] α -BTX binding assay, centrifuged for 20 minutes at 12,000

x g, washed twice. and then re-suspended in HB containing 100 μ M diisopropyl fluorophosphate. After 20 minutes at 4° C, membranes (approximately 0.5 mg) were incubated with 3 nM [3H] -(–)-nicotine, test drug, 1 μ M atropine, and either 2 mM CaCl2 or 0.5 mM EGTA for 1 hour at 4° C, and then filtered over Whatman glass fibre filters (thickness C) (pre-treated for 1 hour with 0.5% PEI) using a Brandel cell harvester. Non-specific binding was described by 100 μ M carbachol, and specific binding was typically 84%.

Binding data analysis for Tests A and B

IC50 values and pseudo Hill coefficients (n_H) were calculated using the non-linear curve fitting program ALLFIT (DeLean A, Munson P J and Rodbard D (1977) Am. J. Physiol., 235:E97-E102). Saturation curves were fitted to a one site model, using the non-linear regression program ENZFITTER (Leatherbarrow, R.J. (1987)), yielding K_D values of 1.67 and 1.70 nM for the 125I-α -BTX and [3H] -(–)-nicotine ligands respectively. K_i values were estimated using the general Cheng-Prusoff equation:

$$K_i=[\ IC_{50}]\ /((2+([\text{ligand}]\ /K_D]\ )^n)^{1/n}-1)$$

where a value of n=1 was used whenever $n_H < 1.5$ and a value of n=2 was used when $n_H \geq 1.5$. Samples were assayed in triplicate and were typically ± 5%. K_i values were determined using 6 or more drug concentrations. The compounds of the invention are compounds with binding affinities (K_i) of less than 10μM in either Test A or Test B, indicating that they are expected to have useful therapeutic activity.

The compounds of the invention have the advantage that they may be less toxic, be more efficacious, be longer acting, have a broader range of activity, be more potent, produce fewer side effects, are more easily absorbed or have other useful pharmacological properties.

General Experimental Procedures

Commercial reagents were used without further purification. Mass spectra were recorded using either a Hewlett Packard 5988A or a MicroMass Quattro-1 Mass Spectrometer and are reported as *m/z* for the parent molecular ion. Room temperature refers to 20–25 °C.

EXAMPLES

The following examples are preferred non-limiting examples embodying preferred aspects of the invention.

Intermediate 1

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-bromofuran-2-carboxamide)

A mixture of *(R)*-1-azabicyclo[2.2.2]oct-3-ylamine dihydrochloride (655 mg), 5-bromofuran-2-carboxylic acid (681 mg), 1-hydroxybenzotriazole hydrate (457 mg), *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (1.069 g), and *N,N*-diisopropylethylamine (2.5 mL) in *N,N*-dimethylformamide (10 mL) was agitated until a homogenous solution was obtained, and was then allowed to stand at room temperature overnight. The solution was evaporated, and the residue was partitioned between aqueous sodium hydroxide and chloroform. The chloroform layer was dried over magnesium sulfate, filtered, and evaporated and the residue was purified by chromatography on silica gel in a solid phase extraction cartridge using ammoniated methanol / chloroform mixtures as the eluent. The compound was then dissolved in tetrahydrofuran (20 mL), excess hydrogen chloride (5 mL; 1M solution in diethyl ether) was added, and the solution was evaporated and then recrystallised from methanol / diethyl ether to give the hydrochloride salt of the title compound as a colourless solid (538 mg); MS (ES^+) 299, 301 (MH^+).

Intermediate 2

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-bromothiophene-2-carboxamide)

A mixture of *(R)*-1-azabicyclo[2.2.2]oct-3-ylamine dihydrochloride (4 g), 5-bromothiophene-2-carboxylic acid (4.25 g), 1-hydroxybenzotriazole hydrate (2.77 g), *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (6.6 g), and *N,N*-diisopropylethylamine (14 mL), in *N,N*-dimethylformamide (100 mL) was stirred at room temperature overnight. The solution was evaporated, and the residue was partitioned between aqueous sodium hydroxide and chloroform. The chloroform layer was dried over magnesium sulfate, filtered, and evaporated. The residue was purified by flash chromatography on silica gel and eluted with 5%-20% 3.5N methanolic ammonia / chloroform mixtures. Evaporation of solvent gave yellow solid (5.87 g); MS (ES^+) 315, 317 (MH^+).

Intermediate 3

(S)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-bromothiophene-2-carboxamide)

A mixture of *(S)-N*-1-azabicyclo[2.2.2]oct-3-ylamine dihydrochloride (1.9 g), 5-bromothiophene-2-carboxylic acid (1.97 g), 1-hydroxybenzotriazole hydrate (1.28 g), *O*-

benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (3.06 g), and *N,N*-diisopropylethylamine (8.3 mL) in *N,N*-dimethylformamide (20 mL) was stirred at room temperature overnight. The solution was evaporated, and the residue was partitioned between aqueous sodium hydroxide and chloroform. The chloroform layer was dried (Mg_2SO_4), filtered, and evaporated. The residue was purified by flash chromatography on silica gel and eluted with 5%-20% 3.5M methanolic ammonia / chloroform mixtures. Evaporation of solvent gave white solid (3 g); MS (ES^+) 315, 317 (MH^+).

Intermediate 4

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-bromobenzamide)

Prepared by a method analogous to that described for the preparation of Intermediate 1 from *(R)*-1-azabicyclo[2.2.2]oct-3-ylamine dihydrochloride and 3-bromobenzoic acid; the compound was purified by chromatography on silica gel using ammoniated methanol/chloroform mixtures as the eluent. The compound was then dissolved in tetrahydrofuran, excess hydrogen chloride (1M solution in diethyl ether) was added, and the solution was evaporated and then recrystallised from methanol / diethyl ether to give the hydrochloride salt of the title compound as a colourless solid; MS (ES^+) 309, 311 (MH^+).

Intermediate 5

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(4-bromobenzamide)

Prepared by a method analogous to that described for the preparation of Intermediate 1 from *(R)*-1-azabicyclo[2.2.2]oct-3-ylamine dihydrochloride and 4-bromobenzoic acid; the compound was purified by chromatography on silica gel using ammoniated methanol / chloroform mixtures as the eluent. The compound was then dissolved in tetrahydrofuran, excess hydrogen chloride (1M solution in diethyl ether) was added, and the solution was evaporated and then recrystallised from methanol / t-butyl methyl ether to give the hydrochloride salt of the title compound as a colourless solid; MS (ES^+) 309, 311 (MH^+).

Intermediate 6

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-iodobenzamide)

Prepared by a method analogous to that described for the preparation of Intermediate 1 from *(R)*-1-azabicyclo[2.2.2]oct-3-ylamine dihydrochloride and 3-iodobenzoic acid; the compound was purified by solid phase extraction on silica gel using ammoniated methanol / chloroform mixtures as the eluent followed by reverse phase

HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. The product-containing fractions were evaporated, the residue was dissolved in methanol, excess hydrogen chloride solution (4M in 1,4-dioxane) was added and the solution was evaporated to give the hydrochloride salt of the title compound as a colourless solid; MS (ES^+) 357 (MH^+).

Intermediate 7

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(4-iodobenzamide)

Prepared by a method analogous to that described for the preparation of Intermediate 1 from *(R)*-1-azabicyclo[2.2.2]oct-3-ylamine dihydrochloride and 4-iodobenzoic acid; the compound was purified by solid phase extraction on silica gel using ammoniated methanol / chloroform mixtures as the eluent followed by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. The product-containing fractions were evaporated, the residue was dissolved in methanol, excess hydrogen chloride solution (4M in 1,4-dioxane) was added and the solution was evaporated to give the hydrochloride salt of the title compound as a colourless solid; MS (ES^+) 357 (MH^+).

Intermediate 8

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(4-bromothiophene-2-carboxamide)

(A) 4-Bromothiophene-2-carboxylic acid

Chromium (VI) oxide (20 g), and concentrated sulfuric acid (32 g) were dissolved in water (50 mL) and when dissolution was complete, the volume was made up to 100 mL with water. 55 mL of the resulting solution was added dropwise to a solution of 4-bromothiophene-2-carboxaldehyde (19.1 g) in acetone (200 mL) stirred at 0 °C. After 2h, the solution was diluted with water and extracted with chloroform. The organic extracts were washed with water, then extracted with aqueous sodium hydroxide. The alkaline mixture was acidified by cautious addition of concentrated hydrochloric acid then extracted with chloroform. The organic layer was then dried(Mg_2SO_4), filtered, and evaporated. The resulting solid was recrystallised from diethyl ether/hexane to give a colourless solid; MS (ES^+) 207, 209 (MH^+).

(B) *(R)-N-*(1-Azabicyclo[2.2.2]oct-3-yl)(4-bromothiophene-2-carboxamide)

Prepared by a method analogous to that described for the preparation of Intermediate 1 from *(R)*-1-azabicyclo[2.2.2]oct-3-ylamine dihydrochloride and 4-bromothiophene-2-carboxylic acid. The residue from evaporation of the reaction mixture

was partitioned between aqueous hydrochloric acid and chloroform. The aqueous layer was then basified with aqueous sodium hydroxide and extracted with chloroform. The organic extracts were dried ($MgSO_4$), filtered, and evaporated and resulting solid was recrystallised from ethyl acetate/hexane to give the title compound as a colourless solid; MS (ES^+) 315, 317 (MH^+).

Intermediate 9

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-bromothiophene-3-carboxamide)

(A) 5-Bromothiophene-3-carboxylic acid

Bromine (46.5 g) in acetic acid (200 mL) was added dropwise to a solution of thiophene-3-carboxylic acid (38 g) in acetic acid (300 mL). After the addition was complete, stirring was continued at room temperature for 30min. The reaction mixture was poured into 2000 mL of ice/water and the precipitated solid was collected and recrystallised from water to give a colourless solid; MS (ES^-) 205, 207 (MH^+).

(B) *(R)-N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-bromothiophene-3-carboxamide)

Prepared by a method analogous to that described for the preparation of Intermediate 1 from *(R)*-1-azabicyclo[2.2.2]oct-3-ylamine dihydrochloride and 5-bromothiophene-3-carboxylic acid. The compound was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. The product-containing fractions were evaporated, the residues dissolved in methanol, excess hydrogen chloride solution (4M in 1,4-dioxane) was added and the solution was evaporated. After drying under vacuum, the hydrochloride salt of the title compound was obtained as a colourless solid; MS (ES^+) 315, 317 (MH^+).

Example 1

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-phenylfuran-2-carboxamide)

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-bromofuran-2-carboxamide) hydrochloride (100 mg), phenylboronic acid (45 mg), tetrakis(triphenylphosphine)palladium(0) (20 mg), cesium carbonate (547 mg), in a mixture of 1,2-dimethoxyethane (6 mL), ethanol (1.5 mL) and water (1 mL) were stirred under reflux under a nitrogen atmosphere for 17 h. The solution was evaporated and the residue was dissolved in chloroform. The solution was washed with aqueous sodium carbonate and the organic layer was then dried (Mg_2SO_4), filtered, and evaporated. HPLC purification using a gradient of 1:1 ammoniated methanol in chloroform, and chloroform gave the title compound as a colourless solid (63 mg); MS (ES^+) 297 (MH^+).

Example 2

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-fluorophenyl)furan-2-carboxamide)

Prepared by a method analogous to that described in Example 1 from *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-bromofuran-2-carboxamide) and 3-fluorobenzeneboronic acid, using tetrakis(triphenylphosphine)palladium(0) and sodium carbonate in a mixture of 1,2-dimethoxyethane and water. The compound was purified by filtration through a silica gel solid phase extraction cartridge using ammoniated methanol/chloroform mixtures as the eluent, and then by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. Evaporation of solvent gave the trifluoroacetate salt of the title compound as a colourless solid; MS (ES^+) 315 (MH^+).

Example 3

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(3-thienyl)benzamide)

Prepared by a method analogous to that described in Example 1 from *(R)*-1-azabicyclo[2.2.2]oct-3-yl)(3-bromobenzamide) and 3-thiopheneboronic acid, using tetrakis(triphenylphosphine)palladium (0) and sodium carbonate in a mixture of tetrahydrofuran, ethanol, and water. The compound was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. Evaporation of solvent gave the trifluoroacetate of the title compound as a colourless solid; MS (ES^+) 313 (MH^+).

Example 4

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-phenylbenzamide)

Prepared by a method analogous to that described in Example 1 from *(R)*-1-azabicyclo[2.2.2]oct-3-yl)(3-bromobenzamide) and phenylboronic acid, using tetrakis(triphenylphosphine)palladium(0) and sodium carbonate in a mixture of tetrahydrofuran, ethanol, and water. The compound was purified by flash chromatography on silica gel and eluted with 3%-10% 3.5N methanolic ammonia / chloroform mixtures. Evaporation of solvent gave the title compound as a colourless solid; MS (ES^+) 307 (MH^+).

Example 5

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(3-pyridyl)benzamide)

Prepared by a method analogous to that described in Example 1 from *(R)*-1-azabicyclo[2.2.2]oct-3-yl)(3-bromobenzamide) and pyridine-3-boronic acid, using tetrakis(triphenylphosphine)palladium(0) and sodium carbonate in a mixture of

tetrahydrofuran, ethanol, and water. The compound was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. The product-containing fractions were then evaporated and the residue dissolved in methanol. Excess hydrogen chloride solution (1M in diethyl ether) was added and the solution was evaporated. After drying under vacuum, the dihydrochloride salt of the title compound was obtained as a colourless solid; MS (ES^+) 308 (MH^+).

Example 6

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-2-carboxamide)

Prepared by a method analogous to that described in Example 1 from *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-bromothiophene-2-carboxamide) and phenylboronic acid, using tetrakis(triphenylphosphine)palladium(0) and sodium carbonate in a mixture of tetrahydrofuran, ethanol, and water. The compound was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. Evaporation of the product-containing fractions gave the trifluoroacetate salt of the title compound as a colourless solid; MS (ES^+) 313 (MH^+).

Example 7

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(3-methoxyphenyl)benzamide)

Prepared by a method analogous to that described in Example 1 from *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-bromobenzamide) and 3-methoxyphenylboronic acid, using tetrakis(triphenylphosphine)palladium(0) and cesium carbonate in a mixture of 1,2-dimethoxyethane and water. The compound was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. Evaporation of the product-containing fractions gave the trifluoroacetate salt of the title compound as a colourless solid; MS (ES^+) 337 (MH^+).

Example 8

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(2-methoxyphenyl)benzamide)

Prepared by a method analogous to that described in Example 1 from *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-bromobenzamide) and 2-methoxyphenylboronic acid, using tetrakis(triphenylphosphine)palladium(0) and cesium carbonate in a mixture of 1,2-dimethoxyethane and water . The compound was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous

trifluoroacetic acid as the eluent. Evaporation of the product-containing fractions gave the trifluoroacetate salt of the title compound as a colourless solid; MS (ES^+) 337 (MH^+).

Example 9

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(3-(*N*-acetylamino)phenyl)benzamide)

Prepared by a method analogous to that described in Example 1 from *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-bromobenzamide) and 3-(*N*-acetylamino)phenylboronic acid, using tetrakis(triphenylphosphine)palladium(0) and cesium carbonate in a mixture of 1,2-dimethoxyethane and water. The compound was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. Evaporation of the product-containing fractions gave the trifluoroacetate salt of the title compound as a colourless solid; MS (ES^+) 364 (MH^+).

Example 10

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(3-fluorophenyl)benzamide)

Prepared by a method analogous to that described in Example 1 from *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-bromobenzamide) and 3-fluorobenzeneboronic acid, using tetrakis(triphenylphosphine)palladium(0) and cesium carbonate in a mixture of 1,2-dimethoxyethane and water. The compound was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. Evaporation of the product-containing fractions gave the trifluoroacetate salt of the title compound as a colourless solid; MS (ES^+) 325 (MH^+).

Example 11

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(3-methylphenyl)benzamide)

Prepared by a method analogous to that described in Example 1 from *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-bromobenzamide) and 3-methylphenylboronic acid, using tetrakis(triphenylphosphine)palladium(0) and cesium carbonate in a mixture of 1,2-dimethoxyethane and water. The compound was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. Evaporation of the product-containing fractions gave the trifluoroacetate salt of the title compound as a colourless solid; MS (ES^+) 321(MH^+).

Example 12

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(2-thienyl)benzamide)

Prepared by a method analogous to that described in Example 1 from *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-bromobenzamide) and 2-thiopheneboronic acid, using

tetrakis(triphenylphosphine)palladium(0), cesium carbonate in a mixture of 1,2-dimethoxyethane and water. The compound was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. Evaporation of the product-containing fractions gave the trifluoroacetate salt of the title compound as a colourless solid; MS (ES^+) (MH^+).

Example 13

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(3,5-dichlorophenyl)benzamide)

Prepared by a method analogous to that described in Example 1 from *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-bromobenzamide) and 3,5-dichlorophenylboronic acid, tetrakis(triphenylphosphine)palladium(0), cesium carbonate in a mixture of 1,2-dimethoxyethane and water. The compound was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. Evaporation of the product-containing fractions gave the trifluoroacetate salt of the title compound as a colourless solid; MS (ES^+) 375,377MH^+).

Example 14

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(2-naphthyl)benzamide)

Prepared by a method analogous to that described in Example 1 from *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-bromobenzamide) and 2-naphthaleneboronic acid, tetrakis(triphenylphosphine)palladium(0), cesium carbonate in a mixture of 1,2-dimethoxyethane and water. The compound was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. Evaporation of the product-containing fractions gave the trifluoroacetate salt of the title compound as a colourless solid; MS (ES^+) 357(MH^+).

Example 15

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(4-fluorophenyl)benzamide)

Prepared by a method analogous to that described in Example 1 from *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-bromobenzamide) and 4-fluorophenylboronic acid, using tetrakis(triphenylphosphine)palladium(0) and cesium carbonate in a mixture of 1,2-dimethoxyethane and water. The compound was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. Evaporation of the product-containing fractions gave the trifluoroacetate salt of the title compound as a colourless solid; MS (ES^+) 325 (MH^+).

Example 16

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)furan-2-carboxamide)

Prepared by a method analogous to that described in Example 1 from *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-bromofuran-2-carboxamide) and pyridine-3-boronic acid, using tetrakis(triphenylphosphine)palladium(0) and sodium carbonate in a mixture of tetrahydrofuran, ethanol and water. The compound was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. The product-containing fractions were then evaporated and the residue dissolved in methanol. Excess hydrogen chloride solution (1M in diethyl ether) was added and the solution was evaporated. After drying under vacuum, the dihydrochloride salt of the title compound was obtained as a colourless solid; MS (ES^+) 298 (MH^+).

Example 17

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-thienyl)furan-2-carboxamide)

Prepared by a method analogous to that described in Example 1 from *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-bromofuran-2-carboxamide) and 3-thiopheneboronic acid, tetrakis(triphenylphosphine)palladium(0), sodium carbonate in a mixture of tetrahydrofuran, ethanol and water. The compound was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. Evaporation of the product-containing fractions gave the trifluoroacetate salt of the title compound as a colourless solid; MS (ES^+) 303(MH^+).

Example 18

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-benzo[b]furanyl)furan-2-carboxamide)

Prepared by a method analogous to that described in Example 1 from *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-bromofuran-2-carboxamide) and benzo[b]furan-2-boronic acid, using tetrakis(triphenylphosphine)palladium(0) and sodium carbonate in a mixture of tetrahydrofuran, ethanol and water. The compound was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. Evaporation of the product-containing fractions gave the trifluoroacetate salt of the title compound as a colourless solid; MS (ES^+) 337(MH^+).

Example 19

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)furan-2-carboxamide)

Prepared by a method analogous to that described in Example 1 from *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-bromofuran-2-carboxamide) and pyridine-4-boronic acid, using tetrakis(triphenylphosphine)palladium(0) and sodium carbonate in a mixture of 1,2-dimethoxyethane and water. The compound was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. The product-containing fractions were then evaporated and the residue dissolved in methanol. Excess hydrogen chloride solution (1M in diethyl ether) was added and the solution was evaporated. After drying under vacuum, the dihydrochloride salt of the title compound was obtained as a colourless solid; MS (ES^+) 298 (MH^+).

Example 20

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-thienyl)furan-2-carboxamide)

Prepared by a method analogous to that described in Example 1 from *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-bromofuran-2-carboxamide) and 2-thiopheneboronic acid, using tetrakis(triphenylphosphine)palladium(0) and sodium carbonate in a mixture of tetrahydrofuran, ethanol and water. The compound was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. Evaporation of the product-containing fractions gave the trifluoroacetate salt of the title compound as a colourless solid; MS (ES^+) 303(MH^+).

Example 21

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-methoxyphenyl)furan-2-carboxamide)

Prepared by a method analogous to that described in Example 1 from *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-bromofuran-2-carboxamide) and 3-methoxyphenylboronic acid, using tetrakis(triphenylphosphine)palladium (0) and sodium carbonate in a mixture of tetrahydrofuran, ethanol and water. The compound was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. Evaporation of the product-containing fractions gave the trifluoroacetate salt of the title compound as a colourless solid; MS (ES^+) 327 (MH^+).

Example 22

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-methoxyphenyl)furan-2-carboxamide)

Prepared by a method analogous to that described in Example 1 from *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-bromofuran-2-carboxamide) and 2-methoxyphenylboronic acid, using tetrakis(triphenylphosphine)palladium(0) and sodium carbonate in a mixture of

tetrahydrofuran, ethanol and water. The compound was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. Evaporation of the product-containing fractions gave the trifluoroacetate salt of the title compound as a colourless solid; MS (ES^+) 327 (MH^+).

Example 23

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(4-fluorophenyl)furan-2-carboxamide)

Prepared by a method analogous to that described in Example 1 from *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-bromofuran-2-carboxamide) and 4-fluorophenylboronic acid, using tetrakis(triphenylphosphine)palladium(0) and sodium carbonate in a mixture of tetrahydrofuran, ethanol and water. The compound was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. Evaporation of the product-containing fractions gave the trifluoroacetate salt of the title compound as a colourless solid; MS (ES^+) 315 (MH^+).

Example 24

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-naphthyl)furan-2-carboxamide)

Prepared by a method analogous to that described in Example 1 from *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-bromofuran-2-carboxamide) and 2-naphthaleneboronic acid, using tetrakis(triphenylphosphine)palladium(0) and cesium carbonate in a mixture of 1,2-dimethoxyethane and water . The compound was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. Evaporation of the product-containing fractions gave the trifluoroacetate salt of the title compound as a colourless solid; MS (ES^+) 347 (MH^+).

Example 25

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-methylphenyl)furan-2-carboxamide)

Prepared by a method analogous to that described in Example 1 from *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-bromofuran-2-carboxamide) and 3-methylphenylboronic acid, using tetrakis(triphenylphosphine)palladium(0) and cesium carbonate in a mixture of 1,2-dimethoxyethane and water. The compound was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. Evaporation of the product-containing fractions gave the trifluoroacetate salt of the title compound as a colourless solid; MS (ES^+) 311 (MH^+).

Example 26

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-furyl)furan-2-carboxamide)

Prepared by a method analogous to that described in Example 1 from *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-bromofuran-2-carboxamide) and 3-furanboronic acid, using tetrakis(triphenylphosphine)palladium (0) and cesium carbonate in a mixture of 1,2-dimethoxyethane and water . The compound was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. Evaporation of the product-containing fractions gave the trifluoroacetate salt of the title compound as a colourless solid; MS (ES^+) 287 (MH^+).

Example 27

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-furyl)furan-2-carboxamide)

A mixture of *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-bromofuran-2-carboxamide) (146 mg), 2-(tri-n-butylstannyl)furan (0.15 mL), tris(dibenzylideneacetone)dipalladium(0) (13 mg), lithium chloride (59 mg), and tri(*o*-tolyl)phosphine (44 mg) in 1,2-dimethoxyethane (2 mL) was stirred under reflux under a nitrogen atmosphere for 5h. The solution was filtered and evaporated. The compound was purified by filtration through a silica gel solid phase extraction cartridge using ammoniated methanol / chloroform mixtures as the eluent, and then by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. Evaporation of the product-containing fractions gave the trifluoroacetate salt of the title compound as a colourless solid (59 mg); MS (ES^+) 287 (MH^+).

Example 28

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)furan-2-carboxamide)

Prepared by a method analogous to that described in Example 29 from *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-bromofuran-2-carboxamide) and 2-(tri-*n*-butylstannyl)pyridine. The compound was purified by filtration through a silica gel solid phase extraction cartridge using ammoniated methanol/chloroform mixtures as the eluent, and then by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. The product-containing fractions were then evaporated and the residue dissolved in methanol. Excess hydrogen chloride solution (1M in diethyl ether) was added and the solution was evaporated. After drying under vacuum, the dihydrochloride salt of the title compound was obtained as a light yellow solid; MS (ES^+) 298 (MH^+).

Example 29

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiophene-2-carboxamide)

Prepared by a method analogous to that described in Example 1 from *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-bromothiophene-2-carboxamide) and pyridine-4-boronic acid, using tetrakis(triphenylphosphine)palladium(0) and sodium carbonate in a mixture of tetrahydrofuran, ethanol and water. The compound was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. The product-containing fractions were then evaporated and the residue dissolved in methanol. Excess hydrogen chloride solution (1M in diethyl ether) was added and the solution was evaporated. Recrystallisation from methanol / diethyl ether gave the dihydrochloride salt of the title compound as a colourless solid; MS (ES^+) 314 (MH^+).

Example 30

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-2-carboxamide)

Prepared by a method analogous to that described in Example 1 from *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-bromothiophene-2-carboxamide) and pyridine-3-boronic acid, using tetrakis(triphenylphosphine)palladium (0) and sodium carbonate in a mixture of tetrahydrofuran, ethanol and water. The compound was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. The product-containing fractions were then evaporated and the residue dissolved in methanol. Excess hydrogen chloride solution (1M in diethyl ether) was added and the solution was evaporated. Recrystallisation from methanol / diethyl ether gave the dihydrochloride salt of the title compound as a colourless solid; MS (ES^+) 314 (MH^+).

Example 31

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)thiophene-2-carboxamide)

Prepared by a method analogous to that described in Example 27 from *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-bromothiophene-2-carboxamide) and 2-(tri-*n*-butylstannyl)pyridine. The compound was purified by filtration through a silica gel solid phase extraction cartridge using ammoniated methanol / chloroform mixtures as the eluent, and then by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. The product-containing fractions were then evaporated and the residue dissolved in methanol. Excess hydrogen

chloride solution (1M in diethyl ether) was added and the solution was evaporated. Recrystallisation from methanol / diethyl ether gave the dihydrochloride salt of the title compound as a light yellow solid; MS (ES^+) 314 (MH^+).

Example 32

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(4-(2-pyridyl)thiophene-2-carboxamide)

Prepared by a method analogous to that described in Example 27 from *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(4-bromothiophene-2-carboxamide) and 2-(tri-*n*-butylstannyl)pyridine. The compound was purified by filtration through a silica gel solid phase extraction cartridge using ammoniated methanol/chloroform mixtures as the eluent, and then by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. The product-containing fractions were then evaporated and the residue dissolved in methanol. Excess hydrogen chloride solution (1M in diethyl ether) was added and the solution was evaporated. After drying under vacuum, the dihydrochloride salt of the title compound was obtained as a light yellow solid; MS (ES^+) 314 (MH^+).

Example 33

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(4-(4-pyridyl)thiophene-2-carboxamide)

Prepared by a method analogous to that described in Example 1 from *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(4-bromothiophene-2-carboxamide) and pyridine-4-boronic acid, using tetrakis(triphenylphosphine)palladium(0) and sodium carbonate in a mixture of tetrahydrofuran, ethanol and water. The compound was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. The product-containing fractions were then evaporated and the residue dissolved in methanol. Excess hydrogen chloride solution (1M in diethyl ether) was added and the solution was evaporated. After drying under vacuum, the dihydrochloride salt of the title compound was obtained as a colourless solid; MS (ES^+) 314 (MH^+).

Example 34

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(4-(3-pyridyl)thiophene-2-carboxamide)

Prepared by a method analogous to that described in Example 1 from *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(4-bromothiophene-2-carboxamide) and pyridine-3-boronic acid, using tetrakis(triphenylphosphine)palladium (0) and sodium carbonate in a mixture of tetrahydrofuran, ethanol and water. The compound was purified by reverse phase HPLC on

a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. The product-containing fractions were then evaporated and the residue dissolved in methanol. Excess hydrogen chloride solution (1M in diethyl ether) was added and the solution was evaporated. Recrystallisation from methanol / diethyl ether gave the dihydrochloride salt of the title compound as a colourless solid; MS (ES^+) 314 (MH^+).

Example 35

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(N-acetylamino)phenyl)furan-2-carboxamide)

Prepared by a method analogous to that described in Example 1 from *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-bromofuran-2-carboxamide) and 3-(*N*-acetylamino)phenylboronic acid, using tetrakis(triphenylphosphine)palladium (0) and sodium carbonate in a mixture of 1,2-dimethoxyethane and water. The compound was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. The product-containing fractions were then evaporated and the residue dissolved in methanol. Excess hydrogen chloride solution (1M in diethyl ether) was added and the solution was evaporated. Recrystallisation from methanol / diethyl ether gave the hydrochloride salt of the title compound as a yellow solid; MS (ES^+) 354 (MH^+).

Example 36

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-nitrophenyl)furan-2-carboxamide)

Prepared by a method analogous to that described in Example 1 from *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-bromofuran-2-carboxamide) and 3-nitrophenylboronic acid, using tetrakis(triphenylphosphine)palladium(0) and sodium carbonate in a mixture of ethylene glycol dimethyl ether and water. The compound was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. The product-containing fractions were then evaporated and the residue dissolved in methanol. Excess hydrogen chloride solution (1M in diethyl ether) was added and the solution was evaporated. Recrystallisation from methanol / diethyl ether gave the hydrochloride salt of the title compound as a yellow solid; MS (ES^+) 342 (MH^+).

Example 37

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-trifluoromethylphenyl)furan-2-carboxamide)

Prepared by a method analogous to that described in Example 1 from *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-bromofuran-2-carboxamide) and 3-trifluoromethylphenylboronic acid, using tetrakis(triphenylphosphine)palladium(0) and sodium carbonate in a mixture of 1,2-dimethoxyethane and water. The compound was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. The product-containing fractions were then evaporated and the residue dissolved in methanol. Excess hydrogen chloride solution (1M in diethyl ether) was added and the solution was evaporated. After drying under vacuum, the hydrochloride salt of the title compound was obtained as a colourless solid; MS (ES^+) 365 (MH^+).

Example 38

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-chlorophenyl)furan-2-carboxamide)

Prepared by a method analogous to that described in Example 1 from *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-bromofuran-2-carboxamide) and 3-chlorophenylboronic acid, using tetrakis(triphenylphosphine)palladium(0) and sodium carbonate in a mixture of 1,2-dimethoxyethane and water. The compound was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. The product-containing fractions were then evaporated and the residue dissolved in methanol. Excess hydrogen chloride solution (1M in diethyl ether) was added and the solution was evaporated. After drying under vacuum, the hydrochloride salt of the title compound was obtained as a colourless solid; MS (ES^+) 331 (MH^+).

Example 39

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-acetylamino)phenyl)thiophene-2-carboxamide)

Prepared by a method analogous to that described in Example 1 from *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-bromothiophene-2-carboxamide) and 3-(*N*-acetylamino)phenylboronic acid, using tetrakis(triphenylphosphine)palladium (0) and sodium carbonate in a mixture of 1,2-dimethoxyethane and water. The compound was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. Evaporation of the product-containing fractions gave the trifluoroacetate salt of the title compound as a colourless solid; MS (ES^+) 370 (MH^+).

Example 40

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-fluorophenyl)thiophene-2-carboxamide)

Prepared by a method analogous to that described in Example 1 from *(R)-N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-bromothiophene-2-carboxamide) and 3-fluorophenylboronic acid, using tetrakis(triphenylphosphine)palladium (0) and sodium carbonate in a mixture of 1,2-dimethoxyethane and water. The compound was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. Evaporation of the product-containing fractions gave the trifluoroacetate salt of the title compound as a colourless solid; MS (ES^+) 331 (MH^+).

Example 41

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-methoxyphenyl)thiophene-2-carboxamide)

Prepared by a method analogous to that described in Example 1 from *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-bromothiophene-2-carboxamide) and 3-methoxyphenyl-boronic acid, using tetrakis(triphenylphosphine)palladium(0) and sodium carbonate in a mixture of 1,2-dimethoxyethane and water. The compound was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. Evaporation of the product-containing fractions gave the trifluoroacetate salt of the title compound as a colourless solid; MS (ES^+) 343 (MH^+).

Example 42

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-ethoxyphenyl)thiophene-2-carboxamide)

Prepared by a method analogous to that described in Example 1 from *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-bromothiophene-2-carboxamide) and 3-ethoxyphenylboronic acid, using tetrakis(triphenylphosphine)palladium (0) and sodium carbonate in a mixture of tetrahydrofuran, ethanol, and water. The compound was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. Evaporation of the product-containing fractions gave the trifluoroacetate salt of the title compound as a colourless solid; MS (ES^+) 357 (MH^+).

Example 43

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3,5-dimethylisoxazol-4-yl)furan-2-carboxamide)

Prepared by a method analogous to that described in Example 1 from *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-bromofuran-2-carboxamide) and 3,5 dimethylisoxazolyl-4-boronic acid, using tetrakis(triphenylphosphine)palladium(0) and sodium carbonate in a

mixture of 1,2-dimethoxyethane and water. The compound was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. The product-containing fractions were then evaporated and the residue dissolved in methanol. Excess hydrogen chloride solution (1M in diethyl ether) was added and the solution was evaporated. Recrystallisation from methanol / diethyl ether gave the hydrochloride salt of the title compound as a colourless solid; MS (ES^+) 316 (MH^+).

Example 44

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3,5-dimethylisoxazol-4-yl)thiophene-2-carboxamide)

Prepared by a method analogous to that described in Example 1 from *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-bromothiophene-2-carboxamide) and 3,5-dimethylisoxazolyl-4-boronic acid, using tetrakis(triphenylphosphine)palladium (0) and sodium carbonate in a mixture of 1,2-dimethoxyethane and water. The compound was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. The product-containing fractions were then evaporated and the residue dissolved in methanol. Excess hydrogen chloride solution (1M in diethyl ether) was added and the solution was evaporated. Recrystallisation from methanol / diethyl ether gave the hydrochloride salt of the title compound as a colourless solid; MS (ES^+) 332 (MH^+).

Example 45

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-aminophenyl)thiophene-2-carboxamide)

Prepared by a method analogous to that described in Example 1 from *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-bromothiophene-2-carboxamide) and 3-aminophenylboronic acid hydrochloride, using tetrakis(triphenylphosphine)palladium (0) and sodium carbonate in a mixture of 1,2-dimethoxyethane and water. The compound was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. The product-containing fractions were then evaporated and the residue dissolved in methanol. Excess hydrogen chloride solution (1M in diethyl ether) was added and the solution was evaporated. Recrystallisation from methanol / diethyl ether gave the dihydrochloride salt of the title compound as a colourless solid; MS (ES^+) 328 (MH^+).

Example 46

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-3-carboxamide)

Prepared by a method analogous to that described in Example 1 from *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-bromothiophene-3-carboxamide) and pyridine-3-boronic acid, using tetrakis(triphenylphosphine)palladium (0), and sodium carbonate in a mixture of 1,2-dimethoxyethane and water. The compound was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. The product-containing fractions were then evaporated and the residue dissolved in methanol. Excess hydrogen chloride solution (1M in diethyl ether) was added and the solution was evaporated. Recrystallisation from methanol / diethyl ether gave the dihydrochloride salt of the title compound as a colourless solid; MS (ES^+) 314 (MH^+).

Example 47

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(4-chlorophenyl)furan-2-carboxamide)

Prepared by a method analogous to that described in Example 1 from *(R)*-1-azabicyclo[2.2.2]oct-3-ylamine dihydrochloride and 5-(4-chlorophenyl)furoic acid; the compound was purified by chromatography on silica gel using ammoniated methanol/chloroform mixtures as the eluent; MS (ES^+) 331, 333 (MH^+).

Example 48

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiazole-3-carboxamide)

A mixture of *(R)-N*-1-azabicyclo[2.2.2]oct-3-ylamine dihydrochloride (294 mg), 2-(3-pyridyl)thiazole-4-carboxylic acid (304 mg), 1-hydroxybenzotriazole hydrate (199 mg), *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (473 g), and *N,N*-diisopropylethylamine (1.0 mL) in *N,N*-dimethylformamide (10 mL) was stirred at room temperature overnight. The solution was evaporated, and the residue was partitioned between aqueous sodium hydroxide and chloroform. The solution was evaporated and the residue was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. The hydrochloride salt was prepared by evaporation of the product-containing fractions, dissolution of the residue in methanol, addition of excess hydrogen chloride solution (1M in diethyl ether) and evaporation. Recrystallisation from methanol / diethyl ether gave the dihydrochloride salt of the title compound as a colourless solid (428 mg); MS (ES^+) 315 (MH^+).

Example 49

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiazole-3-carboxamide)

A mixture of *(R)-N*-1-azabicyclo[2.2.2]oct-3-ylamine dihydrochloride (236 mg), 2-(4-pyridyl)thiazole-4-carboxylic acid (243 mg), 1-hydroxybenzotriazole hydrate (159 mg), *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (379 mg), and *N,N*-diisopropylethylamine (0.82 mL) in *N,N*-dimethylformamide (10 mL) was stirred at room temperature overnight. The solution was evaporated, and the residue was partitioned between aqueous sodium hydroxide and chloroform. The solution was evaporated and the residue was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. The hydrochloride salt was prepared by evaporation of the product-containing fractions, dissolution of the residue in methanol, addition of excess hydrogen chloride solution (1M in diethyl ether) and evaporation. Recrystallisation from methanol / diethyl ether gave the dihydrochloride salt of the title compound as a colourless solid (428 mg); MS (ES^+) 315 (MH^+).

Example 50

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N,N*-dimethylamino)phenyl)thiophene-2-carboxamide)

Formaldehyde (37% solution in water, 0.18 mL) was added to a solution of *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-aminophenyl)-thiophene-2-carboxamide) (92 mg) in 1% acetic acid in methanol (5 mL). After 30 minutes at room temperature, sodium cyanoborohydride (35 mg) was added, and the reaction mixture was stirred at room temperature for 1h. The solution was evaporated and the residue was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. The hydrochloride salt was prepared by evaporation of the product-containing fractions, dissolution of the residue in methanol, addition of excess hydrogen chloride solution (1M in diethyl ether) and evaporation. Recrystallisation from methanol / diethyl ether gave the dihydrochloride salt of the title compound as a colourless solid (54 mg); MS (ES^+) 356 (MH^+).

Example 51

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(8-quinolinyl)thiophene-2-carboxamide)

Prepared by a method analogous to that described in Example 1 from *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-bromothiophene-2-carboxamide) and 8-quinolineboronic acid ,

tetrakis(triphenylphosphine)palladium (0), sodium carbonate in a mixture of DME, and water . The compound was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. The hydrochloride salt was prepared by evaporation of the product-containing fractions, dissolution of the residue in methanol, addition of excess hydrogen chloride solution (1M in diethyl ether) and evaporation. Recrystallisation from methanol / diethyl ether gave the dihydrochloride salt of the title compound as a colourless solid; MS (ES^+) 364 (MH^+).

Example 52

(S)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-2-carboxamide)

Prepared by a method analogous to that described in Example 1 from *(S)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-bromothiophene-2-carboxamide) and pyridine-3-boronic acid, using tetrakis(triphenylphosphine)palladium (0) and sodium carbonate in a mixture of tetrahydrofuran, ethanol and water. The compound was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. The hydrochloride salt was prepared by evaporation of the product-containing fractions, dissolution of the residue in methanol, addition of excess hydrogen chloride solution (1M in diethyl ether) and evaporation. Recrystallisation from methanol / diethyl ether gave the dihydrochloride salt of the title compound as a colourless solid; MS (ES^+) 314 (MH^+).

Example 53

(S)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiophene-2-carboxamide)

Prepared by a method analogous to that described in Example 1 from *(S)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-bromothiophene-2-carboxamide) and pyridine-4-boronic acid, using tetrakis(triphenylphosphine)palladium (0) and sodium carbonate in a mixture of 1,2-dimethoxyethane and water. The compound was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. The hydrochloride salt was prepared by evaporation of the product-containing fractions, dissolution of the residue in methanol, addition of excess hydrogen chloride solution (1M in diethyl ether) and evaporation. Recrystallisation from methanol / diethyl ether gave the dihydrochloride salt of the title compound as a colourless solid; MS (ES^+) 314 (MH^+).

Example 54

(S)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)thiophene-2-carboxamide)

Prepared by a method analogous to that described in Example 27 from *(S)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-bromothiophene-2-carboxamide) and 2-(tri-*n*-butylstannyl)pyridine. The compound was purified by flash chromatography 5%-20% 3.5N ammoniated methanol / chloroform mixture as eluent. The hydrochloride salt was prepared by evaporation of the product-containing fractions, dissolution of the residue in methanol, addition of excess hydrogen chloride solution (1M in diethyl ether) and evaporation. Recrystallisation from methanol / diethyl ether gave the dihydrochloride salt of the title compound as a colourless solid; MS (ES^+) 314 (MH^+)

Example 55

(S)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-2-carboxamide)

Prepared by a method analogous to that described in Example 1 from *(S)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-bromothiophene-2-carboxamide) and phenylboronic acid, tetrakis(triphenylphosphine)palladium (0) and sodium carbonate in a mixture of tetrahydrofuran, ethanol and water. The compound was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. Evaporation of the product-containing fractions gave the trifluoroacetate salt of the title compound as a colourless solid; MS (ES^+) 313 (MH^+).

Example 56

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-3-carboxamide)

Prepared by a method analogous to that described in Example 1 from *(R)-N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-bromothiophene-3-carboxamide) and phenylboronic acid, using tetrakis(triphenylphosphine)palladium(0), and sodium carbonate in a mixture of tetrahydrofuran, ethanol and water. The compound was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. Evaporation of the product-containing fractions gave the trifluoroacetate salt of the title compound as a colourless solid; MS (ES^+) 313 (MH^+).

Example 57

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(4-phenylthiophene-2-carboxamide)

Prepared by a method analogous to that described in Example 1 from *(R)-N*-(1-Azabicyclo[2.2.2]oct-3-yl)(4-bromothiophene-2-carboxamide) and phenylboronic acid, using tetrakis(triphenylphosphine)palladium (0) and sodium carbonate in a mixture of tetrahydrofuran, ethanol, and water. The compound was purified by reverse phase HPLC

on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. The hydrochloride salt was prepared by evaporation of the product-containing fractions, dissolution of the residue in methanol, addition of excess hydrogen chloride solution (1M in diethyl ether) and evaporation. Recrystallisation from ethyl acetate gave the hydrochloride salt of the title compound as a colourless solid; MS (ES^+) 313 (MH^+).

Example 58

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-cyanophenyl)thiophene-2-carboxamide)

Prepared by a method analogous to that described in Example 1 from *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-bromothiophene-2-carboxamide) and 3-cyanophenylboronic acid, using tetrakis(triphenylphosphine)palladium(0), and sodium carbonate in a mixture of tetrahydrofuran, ethanol and water . The compound was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. The hydrochloride salt was prepared by evaporation of the product-containing fractions, dissolution of the residue in methanol, addition of excess hydrogen chloride solution (1M in diethyl ether) and evaporation. Recrystallisation from methanol / diethyl ether gave the hydrochloride salt of the title compound as a colourless solid; MS (ES^+) 338 (MH^+).

Example 59

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-methylamino)phenyl)thiophene-2-carboxamide)

Sodium methoxide (14 mL, 0.5M solution in methanol) was added to the solution of *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-aminophenyl)thiophene-2-carboxamide) (550 mg) in methanol (5 mL), then paraformaldehyde (117 mg) was added. The mixture was heated under reflux for 1h. After cooling the reaction mixture to room temperature, sodium borohydride (175 mg) was added, and the solution was then heated under reflux for 2h. Aqueous potassium hydroxide (1M, 1.4 mL) was added. Heating under reflux was resumed for 2h and the reaction mixture was then left at room temperature for 16h. The solvent was evaporated and the residue was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. The hydrochloride salt was prepared by evaporation of the product-containing fractions, dissolution of the residue in methanol, addition of excess hydrogen chloride solution (1M in diethyl ether) and evaporation. Recrystallisation from methanol /

diethyl ether gave the dihydrochloride salt of the title compound as a colourless solid (120 mg); MS (ES^+) 342 (MH^+).

Example 60

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-hydroxyphenyl)thiophene-2-carboxamide)

To the (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-methoxyphenyl)thiophene-2-carboxamide) (900 mg), 48% aqueous hydrobromic acid (10 mL) and glacial acetic acid (10 mL) were added. After heating under reflux for 4h, saturated aqueous sodium carbonate and solid sodium carbonate were added to adjust to pH 10. The aqueous layer was extracted with chloroform and the combined extracts were dried over magnesium sulfate. After filtration and evaporation, residue was purified by flash chromatography using 5%-20% 3.5M methanolic ammonia / chloroform mixtures as the eluent. The product obtained was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. The hydrochloride salt was prepared by evaporation of the product-containing fractions, dissolution of the residue in methanol, addition of excess hydrogen chloride solution (1M in diethyl ether) and evaporation. Recrystallisation from methanol / diethyl ether gave the hydrochloride salt of the title compound as a colourless solid (32 mg); MS (ES^+) 329 (MH^+).

Example 61

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridylamino)thiophene-2-carboxamide)

The mixture of *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-bromothiophene-2-carboxamide) (315 mg), 3-aminopyridine (188 mg), tris(dibenzylideneacetone)dipalladium (0) (46 mg), racemic-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (62 mg), and sodium *t*-butoxide (192 mg) in tetrahydrofuran (10 mL) was heated under reflux for 20h. The mixture was filtered and the residue was purified by flash chromatography using 5%-20% 3.5M methanolic ammonia / chloroform mixtures as the eluent. The compound was purified further by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. The hydrochloride salt was prepared by evaporation of the product-containing fractions, dissolution of the residue in methanol, addition of excess hydrogen chloride solution (1M in diethyl ether) and evaporation. Recrystallisation from methanol / diethyl ether gave the dihydrochloride salt of the title compound as a yellow solid (77 mg); MS (ES^+) 329 (MH^+).

Example 62

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-chlorophenyl)thiophene-2-carboxamide)

Prepared by a method analogous to that described in Example 1 from *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-bromothiophene-2-carboxamide) and 3-chlorophenylboronic acid, using tetrakis(triphenylphosphine)palladium (0) and sodium carbonate in a mixture of tetrahydrofuran, ethanol and water . The compound was purified by flash chromatography using a gradient of 5%-20% 3.5M methanolic ammonia / chloroform mixtures as the eluent to give the title compound as a colourless solid; MS (ES^+) 347 (MH^+).

Example 63

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(4-morpholinyl)phenyl)thiophene-2-carboxamide)

A mixture of *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-chlorophenyl)thiophene-2-carboxamide) (0.98 g), morpholine (0.5 mL), tris(dibenzylideneacetone)dipalladium(0) (132 mg), racemic-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (180 mg), and sodium *t*-butoxide (554 mg) in tetrahydrofuran (25 mL) was heated under reflux for 20 hr under nitrogen. The mixture was filtered and the residue was purified by flash chromatography using a gradient of 5%-20% 3.5M methanolic ammonia / chloroform mixtures as the eluent. The mixture was then subjected to reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. The hydrochloride salt was prepared by evaporation of the product-containing fractions, dissolution of the residue in methanol, addition of excess hydrogen chloride solution (1M in diethyl ether) and evaporation. Recrystallisation from methanol / diethyl ether gave the dihydrochloride salt of the title compound as solid (400 mg); MS (ES^+) 398(MH^+).

Example 64

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(aminomethyl)phenyl)thiophene-2-carboxamide)

To the solution of *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-cyanophenyl)thiophene-2-carboxamide) (311 mg) in methanol and acetic acid (1:1, 10 mL) a catalytic amount of 10% Pd-C was added and the mixture was hydrogenated at 50 p.s.i. for 36 hr. The mixture was filtered through a pad of celite. The residue was purified first by flash chromatography using 5-20% 3.5M methanolic ammonia / chloroform mixtures as the eluent and then by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. The free base was prepared by

basification of the product-containing fractions and extraction into chloroform followed by evaporation to gave the title compound (23 mg); MS (ES^+) 342 (MH^+).

Example 65

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-phenoxythiophene-2-carboxamide)

To a solution of *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-bromothiophene-2-carboxamide) (463 mg) in pyridine (10 mL) phenol (158 mg), copper iodide (32 mg) and potassium carbonate (97 mg) were added. The mixture was stirred at 125 °C for 65h under nitrogen. Water was added and the aqueous layer was extracted with chloroform. Following evaporation, the residue was purified by flash chromatography using 5-20% 3.5M methanolic ammonia / chloroform mixtures as the eluent and then by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. The free base was prepared by basification of the product-containing fractions and extraction into chloroform followed by evaporation to gave the title compound (80 mg); MS (ES^+) 329 (MH^+).

Example 66

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-aminophenyl)furan-2-carboxamide)

Prepared by a method analogous to that described in Example 1 from *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-bromofuran-2-carboxamide) and 3-aminophenylboronic acid, using tetrakis(triphenylphosphine)palladium (0) and sodium carbonate in a mixture of tetrahydrofuran, ethanol and water . The compound was purified by flash chromatography using 5-20% 3.5M methanolic ammonia / chloroform mixtures as the eluent and then by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. The free base was prepared by basification of the product-containing fractions and extraction into chloroform followed by evaporation to gave the title compound; MS (ES^+) 312 (MH^+).

Example 67

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N,N*-dimethylamino)phenyl)furan-2-carboxamide)

To the solution of *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-aminophenyl)furan-2-carboxamide) (220 mg) in 1% acetic acid in ethanol (10 mL) formaldehyde (0.26 mL) was added. After 45min, sodium cyanoborohydride (89 mg) was added. The mixture was stirred for 4h. Water was added and the solution was basified to pH>10 by adding solid sodium carbonate. The aqueous layer was extracted chloroform and the extracts were dried

over magnesium sulfate, filtered and evaporated. The compound was purified by flash chromatography using 5-20% 3.5M methanolic ammonia / chloroform mixtures as the eluent. The hydrochloride salt was prepared by evaporation of the product-containing fractions, dissolution of the residue in methanol, addition of excess hydrogen chloride solution (1M in diethyl ether) and evaporation. Recrystallisation from methanol / diethyl ether gave the dihydrochloride salt of the title compound as solid (141 mg); MS (ES^+) 340 (MH^+).

Example 68

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-formylphenyl)thiophene-2-carboxamide)

Prepared by a method analogous to that described in example 1 from *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-bromothiophene-2-carboxamide) and 3-formylphenyl boronic acid , tetrakis(triphenylphosphine)palladium (0), sodium carbonate in a mixture of tetrahydrofuran, ethanol and water . The compound was purified by reverse phase HPLC on a Waters Bondapak® C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluent. The free base was prepared by basification of the product-containing fractions. The aqueous layer was extracted by chloroform and evaporated to gave the title compound; MS (ES^+) 341 (MH^+)

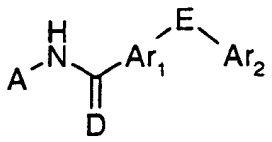
Example 69

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(hydroxymethyl)phenyl)thiophene-2-carboxamide)

To the solution of *(R)-N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-formylphenyl)thiophene-2-carboxamide) (875 mg) in methanol (15 mL), sodium borohydride (97.2 mg) was added. The mixture was then stirred at room temperature for 4h. The residue was partitioned between water and chloroform. The extracts were dried over magnesium sulfate, filtered, and evaporated, and the residue was then purified by flash chromatography using 5-20% 3.5M methanolic ammonia / chloroform mixtures as the eluent to give the title compound (547 mg); MS (ES^+) 343 (MH^+).

CLAIMS

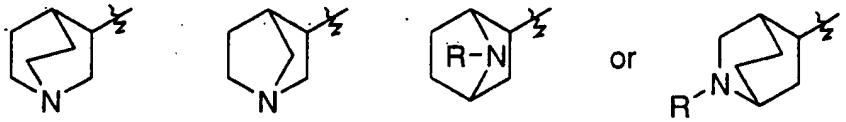
1. A compound of formula I:



I

wherein:

A is



II III IV or V

D is oxygen or sulfur;

E is a single bond, oxygen, sulfur, or NR^{10};

R is hydrogen or methyl;

Ar^1 is a 5- or 6-membered aromatic or heteroaromatic ring containing 0, 1, 2 or 3 nitrogen, oxygen or sulfur atoms, wherein there is no more than 1 oxygen or sulfur atom;

Ar^2 is a 5- or 6-membered aromatic or heteroaromatic ring containing 0, 1, 2 or 3 nitrogen, oxygen or sulfur atoms, wherein there is no more than 2 oxygen or sulfur atom; or an 8-, 9- or 10-membered fused aromatic or heteroaromatic ring system containing 0, 1, 2 or 3 nitrogen, oxygen or sulfur atoms, wherein there is no more than 2 oxygen or sulfur atoms;

wherein when Ar2 is unsubstituted phenyl, Ar^1 is not pyrazolyl;

wherein the aromatic rings Ar^1 and Ar^2 are substituted with 0, 1, 2 or 3 substituents selected from halogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, CN, NO_2, NR^1R^2, $CH_2NR^1R^2$, OR^3, CH_2OR^3, CO_2R^4 and CF_3; but if Ar^1 is phenyl and Ar^2 is quinolynyl, then Ar^2 is substituted with 0, 1, 2 or 3 substituents selected from C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, CN, NO_2, NR^1R^2, $CH_2NR^1R^2$, OR^3, CH_2OR^3 and CO_2R^4;

R^1, R^2, and R^3 are independently C_{1-4}alkyl, aryl, heteroaryl, $C(O)R^5$, $C(O)NHR^6$, $C(O)R^7$, SO_2R^8; or R^1 and R^2 may together be $(CH_2)_jG(CH_2)_k$ where G is oxygen. sulfur, NR^9, or a single bond;

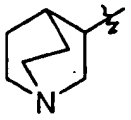
j is 2, 3 or 4;

k is 0, 1 or 2;

R^4, R^5, R^6, R^7, R^8, R^9, and R^{10} are independently C_{1-4}alkyl, aryl, or heteroaryl; or an enantiomer thereof and pharmaceutically acceptable salts thereof;

with the provisos that:

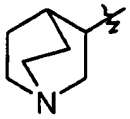
(1) if D represents oxygen, E represents a single bond, and A represents:



II

and either Ar^1 or Ar^2 represents a pyrazole ring , then all optional substituents on the pyrazole ring shall be hydrogen; and

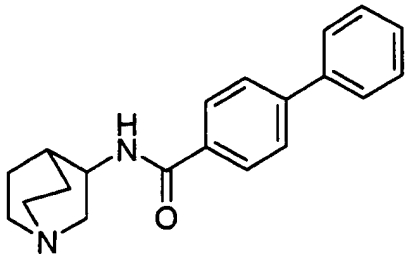
(2) if Ar^1 represents a pyridine ring, Ar^2 represents an aryl ring, and A represents:



II

then all optional substituents on the pyridine ring shall be hydrogen; and

(3) formula I does not represent:

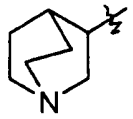


2. A compound according to Claim 1, wherein D represents oxygen.

3. A compound according to Claim 2, wherein E represents a single bond.

4. A compound according to Claim 2, wherein E represents oxygen or NR^{10}.

5. A compound according to Claim 1, wherein A represents



II

6. A compound according to Claim 1, wherein Ar^1 represents a 5- or 6-membered aromatic or heteroaromatic ring containing zero or one nitrogen atom, zero or one oxygen atom, and zero or one sulfur atom; or an enantiomer thereof, and pharmaceutically acceptable salts thereof.

7. A compound according to Claim 5, wherein Ar^1 represents a 5- or 6-membered aromatic or heteroaromatic ring containing zero or one nitrogen atom, zero or one oxygen atom, and zero or one sulfur atom; or an enantiomer thereof, and pharmaceutically acceptable salts thereof.

8. A compound according to Claim 1, wherein Ar^1 represents phenyl, furyl, thiophenyl or thiazolyl.

9. A compound according to Claim 5, wherein Ar^1 represents phenyl, furyl, thiophenyl or thiazolyl.

10. A compound according Claim 1, wherein Ar^2 represents a 5- or 6-membered aromatic or heteroaromatic ring containing zero to three nitrogen atoms, zero or one oxygen atom, and zero or one sulfur atom; or an enantiomer thereof, and pharmaceutically acceptable salts thereof.

11. A compound according Claim 5, wherein Ar^2 represents a 5- or 6-membered aromatic or heteroaromatic ring containing zero to three nitrogen atoms, zero or one oxygen atom, and zero or one sulfur atom; or an enantiomer thereof, and pharmaceutically acceptable salts thereof.

12. A compound according Claim 9, wherein Ar^2 represents a 5- or 6-membered aromatic or heteroaromatic ring containing zero to three nitrogen atoms, zero or one oxygen atom, and zero or one sulfur atom; or an enantiomer thereof, and pharmaceutically acceptable salts thereof.

13. A compound according claim 11 wherein Ar^2 represents a phenyl, furyl, thiophenyl, or pyridinyl.

14. A compound according claim 12 wherein Ar^2 represents a phenyl, furyl, thiophenyl, or pyridinyl.

15. A compound according Claim 1, wherein Ar^1 is substituted with the carboxamide or thiocarboxamide group C(=D)NHA, but no further substituents.

16. A compound according Claim 14, wherein Ar^1 is substituted with the carboxamide or thiocarboxamide group C(=D)NHA, but no further substituents.

17. A compound according to Claim 15, in which the $-EAr^2$ and the carboxamide or thiocarboxamide group C(=D)NHA substituents on Ar^1 are positioned in a 1,3-relationship relative to each other.

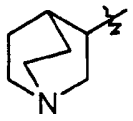
18. A compound according to Claim 16, in which the $-EAr^2$ and the carboxamide or thiocarboxamide group C(=D)NHA substituents on Ar^1 are positioned in a 1,3-relationship relative to each other.

19. A compound according to Claim 1, wherein Ar^1 or Ar^2 is substituted with zero or one substituents selected from: halogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, CN, NO_2, NR^1R^2, $CH_2NR^1R^2$, OR^3, CH_2OR^3, CO_2R^4, and CF_3.

20. A compound according to Claim 14, wherein Ar^1 or Ar^2 is substituted with zero or one substituents selected from: halogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, CN, NO_2, NR^1R^2, $CH_2NR^1R^2$, OR^3, CH_2OR^3, CO_2R^4, and CF_3.

21. A compound according to Claim 1 wherein:

A represents:



II

D represents oxygen;

E represents a single bond;

Ar^1 represents a 5- or 6-membered aromatic or heteroaromatic ring containing zero or one nitrogen atom, zero or one oxygen atom, and zero or one sulfur atom;

Ar^2 represents a 5- or 6-membered aromatic or heteroaromatic ring containing zero to three nitrogen atoms, zero or one oxygen atom, and zero or one sulfur atom;

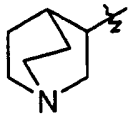
the aromatic ring Ar^1 is substituted with Ar^2 and the carboxamide group C(=O)NHA, but no further substituents; and

Ar^2 is substituted with zero or one substituents selected from: halogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, CN, NO_2, NR^1R^2, $CH_2NR^1R^2$, OR^3, CH_2OR^3, CO_2R^4, and CF_3.

22. A compound according to claim 21, wherein Ar^1 represents a benzene ring, furan ring, or thiophene ring; or an enantiomer thereof, and pharmaceutically acceptable salts thereof.

23. A compound according to Claim 1, wherein:

A represents:



II

D represents oxygen;

E represents a oxygen or NH;

Ar^1 represents a 5- or 6-membered aromatic or heteroaromatic ring containing zero or one nitrogen atom, zero or one oxygen atom, and zero or one sulfur atom;

Ar^2 represents a 5- or 6-membered aromatic or heteroaromatic ring containing zero to three nitrogen atoms, zero or one oxygen atom, and zero or one sulfur atom;

the aromatic ring Ar^1 is substituted with EAr^2 and the C(=O)NHA group, but no further substituents;

Ar^2 is substituted with zero or one substituents selected from halogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, CN, NO_2, NR^1R^2, $CH_2NR^1R^2$, OR^3, CH_2OR^3, CO_2R^4, and CF_3.

24. A compound according to Claim 23, wherein Ar^1 represents a benzene ring, furan ring, or thiophene ring; or an enantiomer thereof, and pharmaceutically acceptable salts thereof.

25. A compound according to Claim 24, in which the EAr2 and the carboxamide group, C(=O)NHA on Ar^1, are positioned in a 1,3-relationship relative to each other; or an enantiomer thereof, and pharmaceutically acceptable salts thereof.

26. A compound according to Claim 1, said compound being selected from the group of:

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-phenylfuran-2-carboxamide);
N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-fluorophenyl)furan-2-carboxamide);
N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(3-thienyl)benzamide);
N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-phenylbenzamide);
N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(3-pyridyl)benzamide);
N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-2-carboxamide);
N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(3-methoxyphenyl)benzamide);
N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(2-methoxyphenyl)benzamide);
N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(3-(*N*-acetylamino)phenyl)benzamide);
N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(3-fluorophenyl)benzamide);
N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(3-methylphenyl)benzamide);
N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(2-thienyl)benzamide);
N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(3,5-dichlorophenyl)benzamide);
N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(2-naphthyl)benzamide);
N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(4-fluorophenyl)benzamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)furan-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-thienyl)furan-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-benzo[b]furanyl)furan-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)furan-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-thienyl)furan-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-methoxyphenyl)furan-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-methoxyphenyl)furan-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(4-fluorophenyl)furan-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-naphthyl)furan-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-methylphenyl)furan-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-furyl)furan-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-furyl)furan-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)furan-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)thiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(4-(2-pyridyl)thiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(4-(4-pyridyl)thiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(4-(3-pyridyl)thiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-acetylamino)phenyl)furan-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-nitrophenyl)furan-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-trifluoromethylphenyl)furan-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-chlorophenyl)furan-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(N-acetylamino)phenyl)thiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-fluorophenyl)thiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-methoxyphenyl)thiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-ethoxyphenyl)thiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3,5-dimethylisoxazol-4-yl)furan-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3,5-dimethylisoxazol-4-yl)thiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-aminophenyl)thiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-3-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(4-chlorophenyl)furan-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiazole-3-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiazole-3-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N,N'*-dimethylamino)phenyl)thiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(8-quinolinyl)thiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-3-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(4-phenylthiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-cyanophenyl)thiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-methylamino)phenyl)thiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-hydroxyphenyl)thiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridylamino)thiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-chlorophenyl)thiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(4-morpholinyl)phenyl)thiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(aminomethyl)phenyl)thiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-phenoxythiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-aminophenyl)furan-2-carboxamide) ;

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N,N*-dimethylamino)phenyl)furan-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-formylphenyl)thiophene-2-carboxamide); and

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(hydroxymethyl)phenyl)thiophene-2-carboxamide);

and pharmaceutically acceptable salts thereof.

27. A compound according to Claim 1, said compound being selected from the group of:

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-phenylfuran-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-fluorophenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(3-thienyl)benzamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(3-phenylbenzamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(3-pyridyl)benzamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(3-methoxyphenyl)benzamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(2-methoxyphenyl)benzamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(3-(*N*-acetylamino)phenyl)benzamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(3-fluorophenyl)benzamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(3-methylphenyl)benzamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(2-thienyl)benzamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(3,5-dichlorophenyl)benzamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(2-naphthyl)benzamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(4-fluorophenyl)benzamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-thienyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-benzo[b]furanyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-thienyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-methoxyphenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-methoxyphenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(4-fluorophenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-naphthyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-methylphenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-furyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-furyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(4-(2-pyridyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(4-(4-pyridyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(4-(3-pyridyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-acetylamino)phenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-nitrophenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-trifluoromethylphenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-chlorophenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-acetylamino)phenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-fluorophenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-methoxyphenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-ethoxyphenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3,5-dimethylisoxazol-4-yl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3,5-dimethylisoxazol-4-yl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-aminophenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-3-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(4-chlorophenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiazole-3-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiazole-3-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N,N*-dimethylamino)phenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(8-quinolinyl)thiophene-2-carboxamide);

(S)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-2-carboxamide);

(S)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiophene-2-carboxamide);

(S)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)thiophene-2-carboxamide);

(S)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-3-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(4-phenylthiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-cyanophenyl)thiophene-2-carboxamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-methylamino)phenyl)thiophene-2-carboxamide);

(R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)(5-(3-hydroxyphenyl)thiophene-2-carboxamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridylamino)thiophene-2-carboxamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-chlorophenyl)thiophene-2-carboxamide);

(R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)(5-(3-(4-morpholinyl)phenyl)thiophene-2-carboxamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(aminomethyl)phenyl)thiophene-2-carboxamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-phenoxythiophene-2-carboxamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-aminophenyl)furan-2-carboxamide) ;

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N,N*-dimethylamino)phenyl)furan-2-carboxamide);

(R)-N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-formylphenyl)thiophene-2-carboxamide); and *(R)-N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(hydroxymethyl)phenyl)thiophene-2-carboxamide);

and pharmaceutically acceptable salts thereof.

28. A compound according to Claim 1, said compound being selected from the group of:

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-phenylfuran-2-carboxamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-fluorophenyl)furan-2-carboxamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(3-thienyl)benzamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-phenylbenzamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-2-carboxamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(3-(*N*-acetylamino)phenyl)benzamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-(2-thienyl)benzamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)furan-2-carboxamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-thienyl)furan-2-carboxamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-benzo[b]furanyl)furan-2-carboxamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-thienyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-methoxyphenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(4-fluorophenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-naphthyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-methylphenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-furyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(4-(2-pyridyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-acetylamino)phenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-nitrophenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-trifluoromethylphenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-chlorophenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-acetylamino)phenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-fluorophenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-methoxyphenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-ethoxyphenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3,5-dimethylisoxazol-4-yl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-aminophenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-3-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(4-chlorophenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*,*N*-dimethylamino)phenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(8-quinolinyl)thiophene-2-carboxamide);

(S)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-2-carboxamide);

(S)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiophene-2-carboxamide);

(S)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)thiophene-2-carboxamide);

(S)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-3-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(4-phenylthiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-cyanophenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-methylamino)phenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-hydroxyphenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridylamino)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(4-morpholinyl)phenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(aminomethyl)phenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-phenoxythiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-aminophenyl)furan-2-carboxamide) ;

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N,N*-dimethylamino)phenyl)furan-2-carboxamide); and

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(hydroxymethyl)phenyl)thiophene-2-carboxamide);

and pharmaceutically acceptable salts thereof.

29. A compound according to Claim 1, said compound being selected from the group:

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-fluorophenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-methoxyphenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(4-fluorophenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-acetylamino)phenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-nitrophenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-trifluoromethylphenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-chlorophenyl)furan-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-acetylamino)phenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-aminophenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-3-carboxamide);

(S)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-2-carboxamide);

(S)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(4-phenylthiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-cyanophenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-hydroxyphenyl)thiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-phenoxythiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-aminophenyl)furan-2-carboxamide); or

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-(3-(hydroxymethyl)phenyl)thiophene-2-carboxamide);

and pharmaceutically acceptable salts thereof.

30. A compound according to any one of Claims 1 to 29, for use in therapy.

31. Use of a compound as defined in any one of claims 1 to 29, in the manufacture of a medicament for the treatment or prophylaxis of psychotic disorders or intellectual impairment disorders.

32. The use of a compound as defined in any one of claims 1 to 29, in the manufacture of a medicament for the treatment or prophylaxis of human diseases or conditions in which activation of the α7 nicotinic receptor is beneficial.

33. The use of a compound as defined in any one of claims 1 to 29, in the manufacture of a medicament for the treatment or prophylaxis of Alzheimer's disease, learning deficit, cognition deficit, attention deficit, memory loss, Lewy Body Dementia, Attention Deficit

Hyperactivity Disorder, anxiety, schizophrenia, mania or manic depression, Parkinson's disease, Huntington's disease, Tourette's syndrome, neurodegenerative disorders in which there is loss of cholinergic synapse, jetlag, cessation of smoking, nicotine addiction including that resulting from exposure to products containing nicotine, pain, or ulcerative colitis.

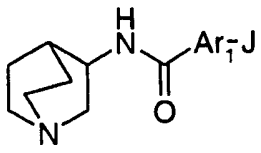
34. A method of treatment or prophylaxis of psychotic disorders or intellectual impairment disorders, which comprises administering a therapeutically effective amount of a compound as defined in any one of Claims 1 to 29.

35. A method of treatment or prophylaxis of human diseases or conditions in which activation of the α7 nicotinic receptor is beneficial which comprises administering a therapeutically effective amount of a compound as defined in any one of Claims 1 to 29.

36. The method according to Claim 35, wherein the disorder is Alzheimer's disease, learning deficit, cognition deficit, attention deficit, memory loss, Lewy Body Dementia, Attention Deficit Hyperactivity Disorder, anxiety, schizophrenia, mania or manic depression, Parkinson's disease, Huntington's disease, Tourette's syndrome, neurodegenerative disorders in which there is loss of cholinergic synapse, jetlag, cessation of smoking, nicotine addiction including that resulting from exposure to products containing nicotine, pain, or ulcerative colitis.

37. A process for the preparation of a compound of formula I, as defined in any one of claims 1 to 29, which comprises:

reacting a compound of formula VI:



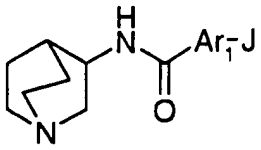
VI

wherein J represents halogen, or OSO_2CF_3 substituent at the position of ring Ar^1 at which the bond to ring Ar^2 is formed with a organometallic compound of formula VII;

VII

in the presence of a organometallic catalyst and solvent.

38. A compound of formula VI:



VI

wherein:

Ar^1 represents a benzene, furan, or thiophene ring;

J represents halogen, or OSO_2CF_3, provided that when Ar^1 represents a benzene ring, J may only represent bromine, iodine, or OSO_2CF_3 in a position meta or para to the carboxamide group;

or an enantiomer thereof, and pharmaceutically acceptable salts thereof.

39. A compound according to claim 38, said compound being selected from the group:

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-bromofuran-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-bromothiophene-2-carboxamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-bromobenzamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(4-bromobenzamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(3-iodobenzamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(4-iodobenzamide);

N-(1-Azabicyclo[2.2.2]oct-3-yl)(4-bromothiophene-2-carboxamide); or

N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-bromothiophene-3-carboxamide);

or an enantiomer thereof, and pharmaceutically acceptable salts thereof.

40. A compound according to claim 38, said compound being selected from the group:

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-bromofuran-2-carboxamide);

(R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-bromothiophene-2-carboxamide);

(S)-N-(1-Azabicyclo[2.2.2]oct-3-yl)(5-bromothiophene-2-carboxamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(3-bromobenzamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(4-bromobenzamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(3-iodobenzamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(4-iodobenzamide);

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(4-bromothiophene-2-carboxamide); or

(R)-*N*-(1-Azabicyclo[2.2.2]oct-3-yl)(5-bromothiophene-3-carboxamide);

or a pharmaceutically acceptable salts thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 01/00329

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 453/02, C07D 453/06, C07D 487/08, A61K 31/439, A61P 25/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0327335 A1 (A.H. ROBINS COMPANY, INCORPORATED), 9 August 1989 (09.08.89), the claims ---	1-40
X	EP 0190920 A2 (A.H. ROBINS COMPANY, INCORPORATED), 13 August 1986 (13.08.86), the claims ---	1-40
X	STN International, file CAPLUS, CAPLUS accession no. 1993:213064, document no. 118:213064, Takeda Chemical Industries, Ltd: "Preparation of five-membered heterocyclic amide derivatives, JP,A2;04247081, 1992.09.03 ---	1-40

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 June 2001	19 -06- 2001
Name and mailing address of the ISA Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Solveig Gustavsson/BS Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 01/00329

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 1416872 A (JOHN WYETH & BROTHER LIMITED), 10 December 1975 (10.12.75), the claims, example 13 --	1-40
A	FR 2529548 A1 (DELALANDE SA), 6 January 1984 (06.01.84) --	1-40
A	STN International, file CAPLUS, CAPLUS accession no. 1996:383036, document no. 125:167754, Brown, George R. et al: "Synthesis and Activity of a Novel Series of 3-Biarylquinuclidine Squalene Synthase Inhibitors, _ J. Med. Chem. (1996), 39(15), 2971-2979 --	1-40
A	EP 0546181 A1 (NIPPON SHINYAKU COMPANY LIMITED), 16 June 1993 (16.06.93), page 7 -- --------	38-40

INTERNATIONAL SEARCH REPORT

In. .ational application No.
PCT/SE01/00329

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 34-36
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Claims 34-36 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

28/05/01

International application No.
PCT/SE 01/00329

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0327335 A1	09/08/89	SE 0327335 T3	
		AT 81457 T	15/10/92
		AU 629197 B	01/10/92
		AU 2950689 A	03/08/89
		CA 1320448 A	20/07/93
		DE 68903178 D,T	18/03/93
		DK 42589 A	02/08/89
		ES 2045402 T	16/01/94
		GR 3006764 T	30/06/93
		IL 88434 A	06/09/92
		JP 1226818 A	11/09/89
		NZ 227794 A	23/12/91
		PH 25906 A	19/12/91
		PT 89575 A,B	04/10/89
		US 4863919 A	05/09/89
		ZA 8809109 A	30/08/89
EP 0190920 A2	13/08/86	SE 0190920 T3	
		AT 88891 T	15/05/93
		AU 589155 B	05/10/89
		AU 5267286 A	07/08/86
		CA 1273297 A	28/08/90
		DE 3688377 A,T	09/06/93
		JP 1932546 C	26/05/95
		JP 6062414 B	17/08/94
		JP 61183223 A	15/08/86
		PH 22646 A	28/10/88
		US 4605652 A	12/08/86
GB 1416872 A	10/12/75	AU 467944 B	18/12/75
		AU 5242173 A	17/10/74
		BE 855713 A	03/10/77
		CH 576964 A	30/06/76
		CH 577476 A	15/07/76
		DE 2311570 A,C	13/09/73
		FR 2181807 A,B	07/12/73
		HK 10279 A	09/03/79
		JP 1283088 C	27/09/85
		JP 49000273 A	05/01/74
		JP 60004187 B	01/02/85
		KE 2916 A	30/03/79
		MY 13779 A	31/12/79
		US 3971787 A	27/07/76
		US 3971789 A	27/07/76
		IN 138602 A	28/02/76

INTERNATIONAL SEARCH REPORT

Information on patent family members

28/05/01

International application No.
PCT/SE 01/00329

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR 2529548 A1	06/01/84	AU 562210 B	04/06/87
		AU 1650783 A	05/01/84
		CA 1265802 A	13/02/90
		DE 3372769 D	00/00/00
		EP 0099789 A,B	01/02/84
		SE 0099789 T3	
		ES 524128 A	16/04/84
		ES 8403897 A	01/07/84
		JP 1879561 C	21/10/94
		JP 5087516 B	16/12/93
		JP 59021684 A	03/02/84
		US 4657911 A	14/04/87
		ZA 8304704 A	28/03/84
EP 0546181 A1	16/06/93	DE 69111816 D,T	30/05/96
		US 5342845 A	30/08/94
		AT 125808 T	15/08/95
		AU 8405891 A	30/03/92
		CA 2090037 A	01/03/92
		WO 9204347 A	19/03/92